

# Human Papillomavirus (HPV): What you need to know

## What is HPV?

Human papillomavirus (HPV) infections are the most common sexually transmitted infections (STIs) in the world. There are over 100 types of human papillomaviruses, and 40 types are known to affect the anus and genital area of humans. It is estimated that around **75% of sexually active Canadians** who have not been immunized against HPV will have an HPV infection at some point in their life. While most HPV infections will go away on their own and not cause any symptoms, infection can sometimes lead to genital warts and cancers.

### You should know

You can be infected with more than one type of HPV at a time.

## What are the symptoms?

Most HPV infections will not cause symptoms, and the body will rid itself of the virus within two years. However, sometimes HPV stays within the body and can lead to genital/anal warts and a variety of cancers, including cervical, penile, head, and neck cancers.

Some types of HPV are classified as **high risk**, as they can lead to cancers of the anus and genital area, cervical cancer, and certain cancers of the head and neck. Some of these high-risk HPV types include types **16, 18, 31, 33, 45, 52, and 58**. These types of HPV do not lead to warts.

Other types are classified as **low risk**, as they do not lead to cancer – but they can lead to lesions such as genital and anal warts. Some of these low-risk HPV types include types **6 and 11**. Warts can range in appearance and size. For example, some warts may appear as small bumps, while others may have a large “cauliflower”-like appearance. The warts caused by HPV do not normally cause discomfort, but they can sometimes become itchy, burn, or bleed.



There are two HPV vaccines approved for use in Canada: the HPV2 vaccine (Cervarix®) and the HPV9 vaccine (Gardasil®). Both vaccines protect against high-risk HPV types 16 and 18 – the two types that cause the majority of HPV-related cancers. The HPV9 vaccine additionally protects against high-risk types 31, 33, 45, 52, and 58, as well as low-risk types 6 and 11.

Vaccine availability differs by province and territory.

## How does it spread?

HPV is mainly spread through sex involving **skin-to-skin** contact, such as frontal/vaginal, oral (performed on the anus or genitals), fingering, and anal, amongst others. HPV can spread from one partner to another, even if the person with HPV has no visible symptoms such as warts. HPV is also spread when someone comes into contact with warts caused by HPV.

Although rare, HPV can also be passed from birthing parent to baby during childbirth, if the birthing parent has genital HPV infection.

## Who is affected by HPV?

Anyone of any **age, gender, or sexual orientation** can get HPV. However, there are some groups that get it more than others. For people who have previously had another sexually transmitted infection (STI) or those who have a weakened immune system (for example, if they have HIV), the chances of getting HPV can be higher.

Gay, bisexual, and other men who have sex with men (gbMSM) get HPV at high rates, including with types 16 and 18, which lead to most HPV-related cancers. There is research that shows that gbMSM are 20 times more likely to develop anal cancer than other men who do not have sex with men. As the HPV vaccine was initially offered only to girls and women in Canada, men may not have received the same messaging around how to protect themselves from HPV. Knowing more about HPV, how it can affect one's health, and how to prevent it can help gbMSM make informed decisions about their sexual health.

As well, gbMSM face other barriers to cancer care and HPV immunization uptake. These barriers include fear — or the experience of discrimination by healthcare professionals and having a previous negative experience with the medical system due to their sexual orientation, among others.



Evidence is also emerging that trans and gender-diverse (TGD) people are more affected by HPV types that can cause cancer at high rates. TGD people face similar barriers to cancer care as those faced by gbMSM, including fear of discrimination and having previous negative experiences with the healthcare system. As well, healthcare professionals generally have a lack of knowledge about TGD-specific cancer care. Knowing about HPV, how it can affect their health, and how to prevent it can help TGD people make informed decisions about their sexual health.

In general, the more sexual partners you have had, the more likely it becomes that you will be exposed to, or will have previously been exposed to, HPV. **Remember, this is a generalized statement, as you can still be exposed to HPV the first time you partake in sexual activities if your partner(s) has/have HPV.**

# Human Papillomavirus (HPV): What you need to know

## Who should be immunized against HPV?

- Adolescents and children as young as 9 years of age, depending on the childhood immunization schedule in their province/territory.
- Adults who have not previously been vaccinated against HPV.
  - Even if you are already sexually active, getting the HPV vaccine can protect you against any HPV types you have not been exposed to.
- Gay, bisexual, and other men who have sex with men (gbMSM).



Publicly funded immunization schedules for HPV may vary between [provinces and territories](#).

### Why is HPV immunization recommended for children starting at the age of nine when they are not sexually active?

Getting vaccinated against HPV before becoming sexually active ensures that when someone does decide to have sex later on in life, they are protected against HPV. Even the first time someone partakes in sexual activities can expose them to HPV, so it is better to protect against HPV infection sooner rather than later.

## Are you protected against HPV?



**HPV vaccines are safe and the most effective way to prevent HPV infection.**

Talk to your doctor, nurse, pharmacist, or local public health office about getting the HPV vaccine for yourself or for your child/adolescent.

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# Mpox (monkeypox) Facts

## About mpox

Mpox is a viral infection that often appears with a rash that may be painful. Most people recover on their own after a few weeks. In some circumstances, people can become very sick and could die.

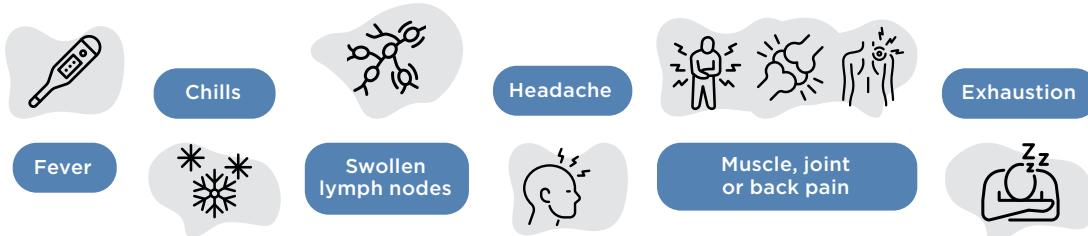
## Symptoms

People usually develop symptoms 5 to 21 days after being exposed to the virus. Symptoms typically last 14 to 28 days.

Symptoms often include a rash or sores that can affect any part of the body, including:

- ⌚ Face and mouth
- ⌚ Arms and legs
- ⌚ Hands and feet
- ⌚ Anus, rectum, and genitals

The rash or sores can be accompanied by general symptoms, such as:



## Mpox symptoms

## How mpox is passed

Mpox can be passed from person-to-person through contact with the lesions or scabs of a person who has mpox. These lesions or scabs may be found on the skin or mucosal surfaces (such as the eyes, mouth, throat, genitals, anus, or rectum).

It may also be possible for it to be passed through:

- ⌚ Contact with bodily fluids, such as blood, saliva, and semen.
- ⌚ Sexual activity, including oral and skin-to-skin contact.
- ⌚ Direct contact with personal items that a person who has mpox uses, such as sex toys, clothing, bedding, towels and toothbrushes.
- ⌚ Respiratory particles from talking, breathing, coughing or sneezing, during close contact.



# Mpox (monkeypox) Facts

Emerging evidence suggests that some people who have mpox may be contagious 1 to 4 days before their symptoms begin. This is known as pre-symptomatic transmission. At this time, it's not yet known how often pre-symptomatic transmission occurs.

There's also a chance that people who are pregnant and have mpox can pass the virus to their fetus through the placenta.

## How mpox spreads

### **Getting tested**

You may be advised to get tested for mpox based on a combination of factors, such as:

- ⌚ Signs and symptoms.
- ⌚ Risk factors, such as exposure to a case or travel history.

Contact a health care provider or your local public health authority for more information on getting assessed and tested.

## Mpox: Getting tested

### **Vaccines and treatment**

The vaccine Imvamune® is authorized by Health Canada for adults 18 years of age and older. Two doses of Imvamune® are recommended for people who are at highest risk of exposure to mpox, before they are exposed to the virus.

This includes:

- ⌚ Men who have sex with men (MSM) and individuals who have sex with MSM and who meet at least one of the following criteria:
  - Having two or more sexual partners or who are in a relationship where at least one of the partners has other sexual partners
  - Having had a confirmed sexually transmitted infection in the past year
- ⌚ Individuals who self-identify as sex workers, regardless of self-identified sex or gender.
- ⌚ Staff or volunteers in sex-on-premises venues where workers may have contact with objects or materials that may be contaminated with the mpox virus without the use of personal protective equipment.

Vaccination is also recommended for people who have had a potential exposure and in settings where transmission is happening. For those who have had a probable exposure, it is important to get vaccinated as soon as possible, ideally within 4 days of exposure. Immunization programs vary across the provinces and territories so reach out to a healthcare provider or your local public health authority to learn more.

Treatment for mpox includes wound care, pain control, and treatment of bacterial superinfections and other complications.

## Mpox: Vaccines and treatment

# Mpox (monkeypox) Facts

## Risks of getting mpox

Most cases in Canada so far are in people with multiple sexual partners, mostly men who report sexual contact with other men. It's important to stress that the risk of exposure to the virus is not limited to any group or setting. Anyone can get or pass on mpox if they come into close contact with someone who has the virus, regardless of sex, race, gender or sexual orientation. We continue to monitor for and investigate cases of mpox in Canada. We will update this information as it becomes available.

### Risks of getting mpox

## Preventing mpox transmission

You can lower your risk of getting or passing on mpox with the following measures:

- ④ Get vaccinated if eligible.
- ④ Avoid sharing lube, sex toys, fetish gear, douching equipment, toothbrushes, substance use equipment like pipes and syringes, bedding, towels and clothing.
  - If sharing, use condoms on sex toys, and change them out between sexual partners.
- ④ Limit your number of sexual partners.
- ④ Avoid close physical contact, including sexual and skin-to-skin contact, with someone who has mpox.
- ④ Check yourself regularly for symptoms like unusual lesions, rash, and fever. If in doubt, isolate from others, get tested, and contact your local health provider for advice.
- ④ Stay home and limit contact with others if you have symptoms, or as recommended by your health care provider.
- ④ Maintain good hand hygiene and respiratory etiquette.
- ④ Clean and disinfect high touch surfaces and objects.
- ④ Stay informed by accessing trusted sources of information.

### Preventing the spread of mpox

## If you have mpox

If you have mpox, your local public health authority may require or suggest you isolate to prevent passing it on to others. Follow their advice on isolation including the length of time they recommend. The isolation period usually ends when the rash has healed (all the scabs have fallen off on their own and the skin is healing).

To lower the risk of passing on the virus to others when isolating, you should **avoid**:

- ④ Leaving your home unless you need urgent medical care.
- ④ Contact with people, especially those who are at risk of more severe disease, such as young children, individuals with weakened immune systems, and anyone who is pregnant.
- ④ Directly touching people, including through sexual contact.
- ④ Contact with animals, including pets, livestock and wildlife, as mpox can be passed from humans to animals.
- ④ Sharing personal items (such as razors, needles, sex toys, and toothbrushes).

# Mpox (monkeypox) Facts

You should also practise the following measures when isolating:

- ④ Wear a well-fitting medical mask when around others.
- ④ Clean your hands and cover coughs and sneezes.
- ④ Clean and disinfect all surfaces and objects that you've had contact with.
- ④ Handle your own laundry and utensils, unless you're unable to do so.
- ④ Do not donate blood or any other bodily fluids (including sperm) or tissue.
- ④ Postpone non-urgent medical visits and procedures.
- ④ Seek advice from a health care provider if you're breastfeeding.

At this time, we're still researching how mpox is transmitted, including the possible risks after a person has recovered. Contact your local public health authority for more information on safer sex practices after recovering from mpox.

## [What to do if you have mpox or if you are providing care at home to someone with mpox](#)

### **If you've been exposed**

Contact your local public health authority if you may have been exposed to someone with mpox. Your local public health authority may also notify you if you've been exposed. They will provide you with instructions on what to do, which may vary depending on your exposure risk level.

In some instances, you may be instructed to get tested for the virus or go to a vaccination clinic to receive a vaccination.

Unless you have been instructed otherwise, you can continue routine daily activities, while taking some precautions for 21 days after you've been exposed:

- ④ Self-monitor for symptoms of mpox.
- ④ Avoid taking medications that are known to lower fever, as they may mask an early symptom of mpox.  
For example, acetaminophen, ibuprofen, and acetylsalicylic acid.
- ④ Continue to cover coughs and sneezes and clean your hands regularly.
- ④ If symptoms develop, isolate immediately, and follow the instructions of your local public health authority.

## [If you've been exposed to mpox](#)



# Condom Fact Sheet In Brief

**Consistent and correct use of the male latex condom reduces the risk of sexually transmitted disease (STD) and human immunodeficiency virus (HIV) transmission.** However, condom use cannot provide absolute protection against any STD. The most reliable ways to avoid transmission of STDs are to abstain from sexual activity, or to be in a long-term mutually monogamous relationship with an uninfected partner. However, many infected persons may be unaware of their infection because STDs often are asymptomatic and unrecognized.

Condom effectiveness for STD and HIV prevention has been demonstrated by both laboratory and epidemiologic studies. Evidence of condom effectiveness is also based on theoretical and empirical data regarding the transmission of different STDs, the physical properties of condoms, and the anatomic coverage or protection provided by condoms.

**Laboratory studies** have shown that latex condoms provide an effective barrier against even the smallest STD pathogens.

**Epidemiologic studies** that compare rates of HIV infection between condom users and nonusers who have HIV-infected sex partners demonstrate that consistent condom use is highly effective in preventing transmission of HIV. Similarly, epidemiologic studies have shown that condom use reduces the risk of many other STDs. However, the exact magnitude of protection has been difficult to quantify because of numerous methodological challenges inherent in studying private behaviors that cannot be directly observed or measured.

**Theoretical and empirical basis for protection:** Condoms can be expected to provide different levels of protection for various STDs, depending on differences in how the diseases or infections are transmitted. Male condoms may not cover all infected areas or areas that could become infected. Thus, they are likely to provide greater protection against STDs that are transmitted only by genital fluids (STDs such as gonorrhea, chlamydia, trichomoniasis, and HIV infection) than against infections that are transmitted primarily by skin-to-skin contact, which may or may not infect areas covered by a condom (STDs such as genital herpes, human papillomavirus [HPV] infection, syphilis, and chancroid).



## HIV Infection

Consistent and correct use of latex condoms is highly effective in preventing sexual transmission of HIV, the virus that causes AIDS.

## Other STDs and Associated Conditions

Consistent and correct use of latex condoms reduces the risk for many STDs that are transmitted by genital fluids (STDs such as chlamydia, gonorrhea, and trichomoniasis).

Consistent and correct use of latex condoms reduces the risk for genital ulcer diseases, such as genital herpes, syphilis, and chancroid, only when the infected area or site of potential exposure is protected.

Consistent and correct use of latex condoms may reduce the risk for genital human papillomavirus (HPV) infection and HPV-associated diseases (e.g., genital warts and cervical cancer).



## Consistent and Correct Condom Use

To achieve maximum protection by using condoms, they must be used consistently and correctly.

The failure of condoms to protect against STD/HIV transmission usually results from inconsistent or incorrect use, rather than product failure.

- **Inconsistent or nonuse** can lead to STD acquisition because transmission can occur with a single sex act with an infected partner.
- **Incorrect use** diminishes the protective effect of condoms by leading to condom breakage, slippage, or leakage. Incorrect use more commonly entails a failure to use condoms throughout the entire sex act, from start (of sexual contact) to finish (after ejaculation).



## How to Use a Condom Consistently and Correctly:



- Use a new condom for every act of vaginal, anal and oral sex—throughout the entire sex act (from start to finish). Before any genital contact, put the condom on the tip of the erect penis with the rolled side out.
- If the condom does not have a reservoir tip, pinch the tip enough to leave a half-inch space for semen to collect. Holding the tip, unroll the condom all the way to the base of the erect penis.
- After ejaculation and before the penis gets soft, grip the rim of the condom and carefully withdraw. Then gently pull the condom off the penis, making sure that semen doesn't spill out.
- Wrap the condom in a tissue and throw it in the trash where others won't handle it.
- If you feel the condom break at any point during sexual activity, stop immediately, withdraw, remove the broken condom, and put on a new condom.
- Ensure that adequate lubrication is used during vaginal and anal sex, which might require water-based lubricants. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, and cooking oil) should not be used because they can weaken latex, causing breakage.

Sources are available at: [www.cdc.gov/condomeffectiveness/brief.html](http://www.cdc.gov/condomeffectiveness/brief.html)



# Sexually Transmitted Infections



Public Health  
Agency of Canada

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**DISCLAIMER:** In the writing of this booklet, a commitment was made to use inclusive language that is relevant to everyone. People use different terms to describe their genitals. This text uses medical terms, such as *vagina* and *penis*, to describe genitals. Cisgender people can often identify with these terms. Some transgender people may use other terms. We acknowledge and respect that people use words that they are most comfortable with.

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# What is an STI?

Sexually transmitted infections, commonly called STI for short, are infections you can get if you have vaginal, oral or anal sex or intimate skin-to-skin contact with someone.

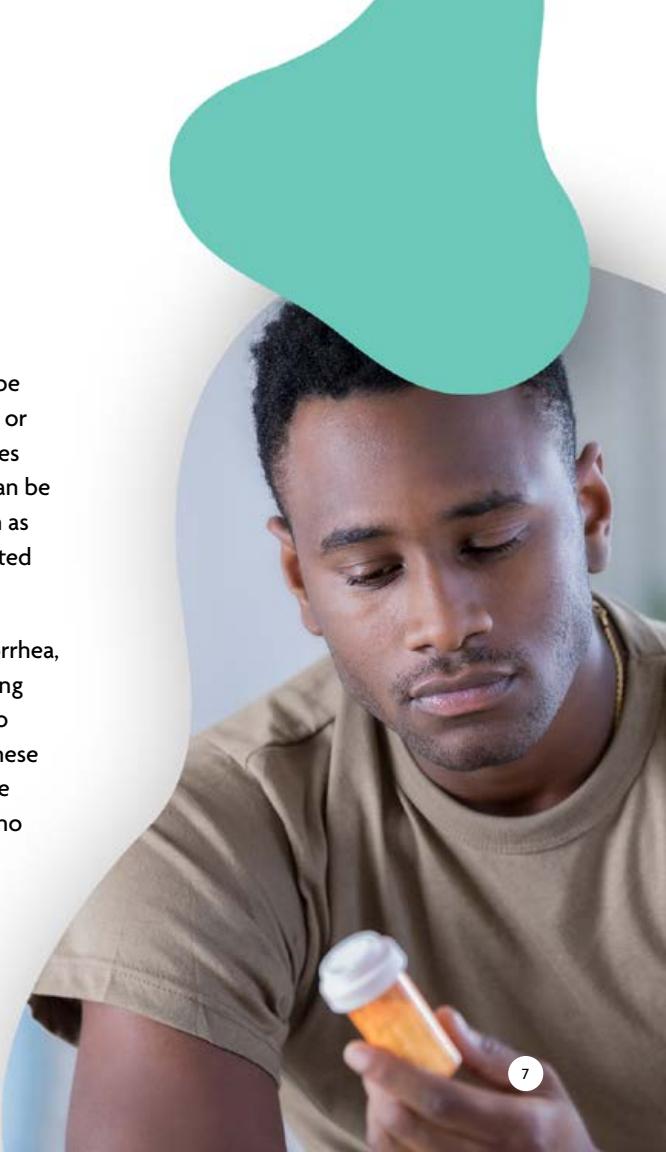
## What are some common STI?

- Chlamydia
- Gonorrhea
- Syphilis
- Trichomoniasis
- Human Immunodeficiency Virus (HIV)
- Herpes Simplex Virus (HSV)
- Hepatitis B
- Human Papillomavirus (HPV)

## Can STI be cured?

There are quite a few STI that can be treated and cured with antibiotics, or a combination of antibiotics. Herpes and HIV can't be cured, but they can be treated effectively. Other STI, such as hepatitis B and HPV can be prevented with vaccines.

However, some STI, including gonorrhea, syphilis, and chlamydia are becoming increasingly difficult to treat due to antibiotic resistance. This means these infections may become untreatable someday because antibiotics may no longer work.



## What are the long-term effects of an untreated STI?

If left untreated or if treatment is not completed, STI can persist or recur, and can cause serious health problems.





### **Long-term effects on your fertility and/or other gynaecological issues: (e.g. chlamydia, gonorrhea)**

- Pelvic inflammatory disease which can cause abscesses and scarring in the vagina, uterus, ovaries and fallopian tubes.
- Ongoing pelvic pain, including painful periods.
- Challenges getting pregnant.
- Ectopic pregnancy, which is a pregnancy that occurs outside the uterus—usually in the fallopian tube. If left untreated the fallopian tube could rupture and cause bleeding that could be life-threatening.

*Make sexual health part of your routine health checkups. Consider whether you want to have sex, practise safer sex, and get tested regularly for STI if you are sexually active.*

### **Long-term effects on your genital area or anus: (e.g. HPV, HSV, LGV)**

- Anogenital warts.
- Pre-cancerous or cancerous cells that can lead to cancers including cancer of the cervix, vulva, vagina, penis, anus or throat and tongue.
- Scarring and/or deformity of the genitals or anus.
- Repeated outbreaks or persistence of the infection throughout life.

### **Long-term effects on your health: (e.g. HIV, hepatitis, syphilis)**

- Untreated HIV can cause a weakened immune system or AIDS.
- Damage to internal organs including the heart, brain and/or liver.
- Cancer of the liver.



Birth control, including the pill, intrauterine devices (IUD/IUS) and other contraceptives, help to protect against pregnancy, not STI.

Birth control is not 100% effective and will only work if used correctly, and consistently.

If you are sexually active, use birth control, make sure you use condoms and/or dental dams, and get tested regularly for STI, including HIV.

A close-up photograph of a person's hand holding a small, rectangular white container. The container has a yellow and blue label with some text and a logo. The background is blurred, showing a dark blue and a teal shape.

Reduce  
your risk



# **Can I get an STI without intercourse if we are just fooling around?**

Yes, you can get some STI just by intimate skin to skin touching or kissing of an infected area.

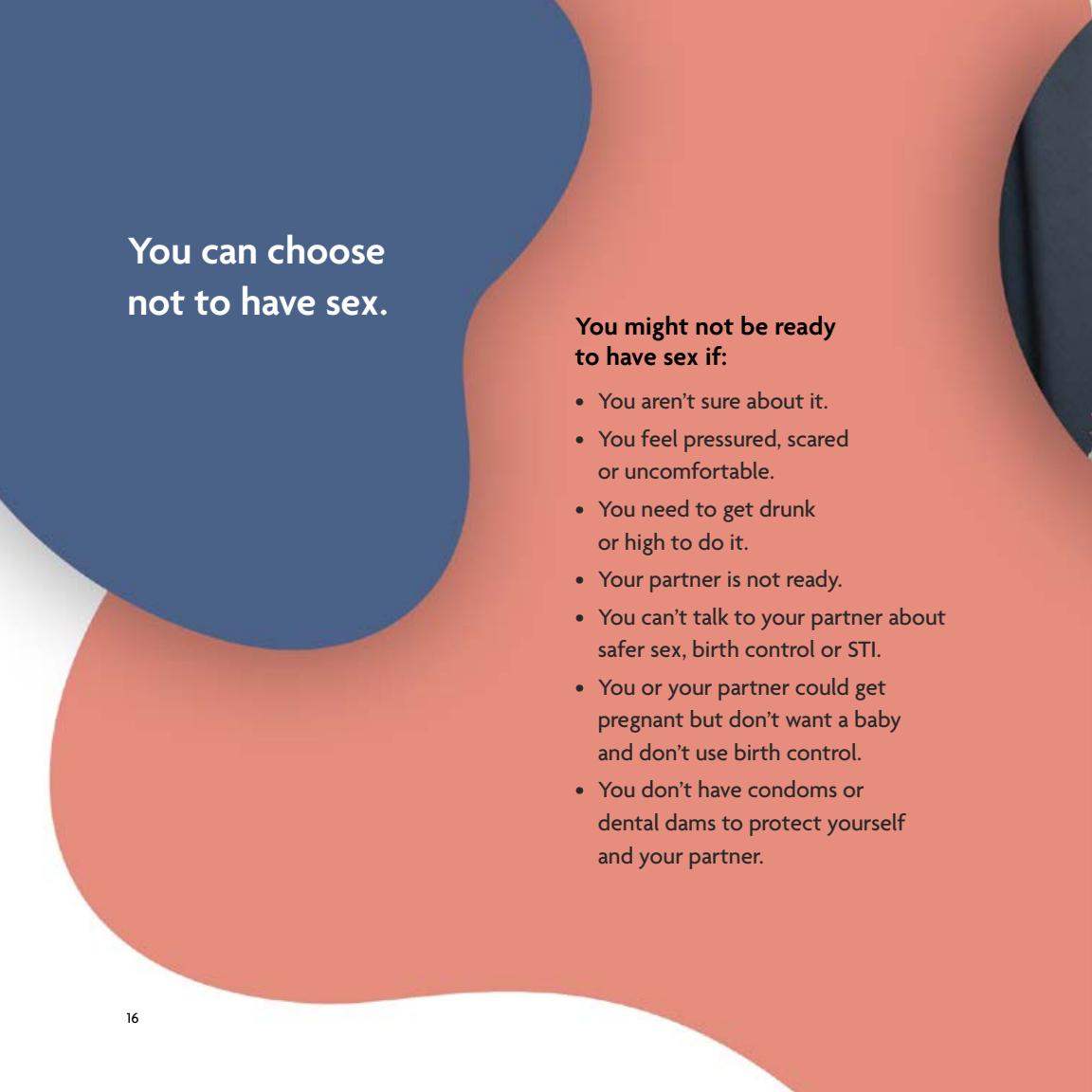
All kinds of sex including oral, vaginal and anal intercourse can transmit infections. They are also contracted through body fluids like blood, semen, saliva, vaginal secretions and breast milk.

It doesn't matter whether you are heterosexual, gay, bisexual, transgender, two-spirit or questioning. STI can be transmitted by anyone.

Drugs and/or alcohol can impair judgement and lead to risky behaviour. When you or your partner are impaired and 'caught up in the moment', you may be more likely to have sex without a condom and take other risks that can increase your exposure to STI and unplanned pregnancy.



*Most STI have no obvious symptoms (or only mild ones), so you may not know if you or your sexual partner has an infection. That's why practising safer sex—always using condoms—and getting tested regularly is so important.*



**You can choose  
not to have sex.**

**You might not be ready  
to have sex if:**

- You aren't sure about it.
- You feel pressured, scared or uncomfortable.
- You need to get drunk or high to do it.
- Your partner is not ready.
- You can't talk to your partner about safer sex, birth control or STI.
- You or your partner could get pregnant but don't want a baby and don't use birth control.
- You don't have condoms or dental dams to protect yourself and your partner.

A photograph of a young couple laughing together. A woman with long blonde hair, wearing a plaid shirt over a white tank top, is on the left. A man with dark skin and short curly hair, wearing a white and black raglan-style shirt, is on the right. They are both smiling and holding hands.

**STI rates are  
the highest**

among Canadians 25 years or younger. If you choose to have sex, remember to always use condoms and/or dental dams.

## What is consent and what is sexual assault?

Consent is when you and your partner feel informed and freely agree to participate in any sexual activity. Your body is yours alone and only you can give your consent.

If one of you is drunk, on drugs, or feels forced, consent has not actually been given. And even if you originally said “yes”, **you can still change your mind**. Saying “no” at any time still means “no.” Any type of sexual activity without your consent or your partner’s consent is sexual assault.



## You may feel pressured to have sex.

Pressure to engage in sexual activity can come from many sources including someone you know well, such as a classmate, friend or partner, someone who has been bullying you (online or in person), or someone you have chatted with or ‘met’ on a dating site or hook-up app.

Sexting is considered a risky sexual activity, even though it isn’t physical, and will not cause an STI. Sexting usually involves sending sexually explicit pictures and/or texts online. Once those images or words are sent, you have no control over whether or not they will be shared with other people.

Visit [sexandu.ca/consent](http://sexandu.ca/consent) for more information on consent, sexual assault and online safety.

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If you think you have been sexually assaulted it’s not your fault – don’t hesitate to seek help. Visit [casac.ca/content/anti-violence-centres](http://casac.ca/content/anti-violence-centres) to find a sexual assault crisis centre near you.

## What should I think about and do before I have sex?

- Talk about safer sex and STI testing with your partner.
- If you or your partner could get pregnant but aren't ready to be parents:
  - Talk about contraception with your partner.
  - Use a tool like [Itsaplan.ca](https://www.itsaplan.ca) to find out the best contraception for you and make an appointment with your healthcare provider.
- Recognize that you shouldn't be judged for your decision to practise safer sex or for asking your partner to do the same.
- Check to see whether you have been vaccinated against HPV. If not, make an appointment with your healthcare provider to discuss vaccination.
- All provinces and territories in Canada give the hepatitis B vaccine to children. If you did not get the vaccine as a child or are unsure, talk to your healthcare provider.



Hepatitis B  
and HPV can be

**prevented by  
a vaccine.**



## Condoms and Dental Dams

Most STI can be prevented by using a condom or dental dam during vaginal, anal or oral sex. You can buy condoms or dental dams at drug stores or health clinics without a prescription. The use of pre-lubricated condoms or added personal lubricants can help prevent the risk of a condom breaking.

Other things to think about:

- Check the expiry date on a condom before using one and make sure the packaging and the condom itself don't have any holes or tears.
- Never use a condom more than once, and don't use two condoms at the same time as that can cause breakage.
- It is recommended to use lubricants with condoms, but be sure to use the right type. Vaseline and other oil-based lubricants destroy latex.

# How to use an external (“male”) condom

External condoms are also known as “male” condoms because they cover the penis during sex. There are three kinds of external condoms: natural, latex and synthetic. Natural condoms help prevent pregnancy but do not protect against STI. To protect against STI, make sure to use a latex or synthetic condom.



## 1 Open Carefully

Do not use teeth, scissors or a knife to open the condom. Roughly tearing or handling the condom can damage it. If the person handling the condom has long fingernails, be extra careful as they can nick the condom, making it ineffective, putting you at risk of STI or unplanned pregnancy.

## 2 Place & Pinch

Put the condom at the tip of the erect penis and pinch out the air at the top. You can also put condoms on sex toys to make sure they won't transmit STI. If the sex toy is inserted in different partners or openings, the condom should be changed.

### 3 Roll It On

Unroll the condom right down to the base of the erect penis or sex toy.

### Afterwards

- 4 The condom user should pull out right after ejaculation and while the penis is still hard. Remember to hold the base of the condom when pulling out so that it does not come off. Throw the used condom in the garbage and do not reuse it.

### Lubricants

It is recommended to use lubricated condoms and, if needed, add a personal lubricant to the outside of the condom to decrease the risk of breaking and to decrease discomfort.

Broken condoms can put you at risk of STI or pregnancy. Only water-based lubricants should be used with latex condoms. Synthetic condoms are fine to use with oil or water-based lubricants.

# How to use an internal (“female”) condom

Internal condoms are also known as “female” condoms because they are inserted in an opening such as the vagina. These condoms are larger than “male” condoms and are pre-lubricated. When used properly, they are highly effective at preventing pregnancy and reducing the risk of STI. They are primarily used for vaginal sex, but they can also be used for anal sex. It is not recommended to use a “male” condom and a “female” condom at the same time as it increases the risk of a condom breaking.

## 1 Open Carefully

Do not use teeth, scissors or a knife to open the condom. Roughly tearing or handling the condom can damage it. If the person handling the condom has long fingernails, be extra careful as they can nick the condom, making it ineffective, putting you at risk of STI or unplanned pregnancy.

## 2 Placement

The outer ring covers the area around the opening of the vagina or anus. The inner ring is used for insertion and to help hold the condom in place during intercourse.

Hold the condom at the closed end, squat, sit or lie comfortably and then slide the inner ring inside. Gently push the inner ring up as far as it will go with the outer ring remaining on the outside. Guide the penis or sex toy to make sure it is entering inside the condom, not next to it.

3

### Afterwards

To remove the condom, twist the outer ring gently and pull the condom out. Throw the used condom in the garbage and do not reuse it.

### Lubricants

“Female” condoms usually come pre-lubricated or with a small package of lubricant. If you need additional lubricant make sure you know what kind of condom you are using first.

For polyurethane condoms, oil-based lubricant products can be used. For latex condoms, use a lubricant made of water, glycol or silicone. The use of the proper lubricant will help avoid breakage and discomfort.

# How to use a dental dam

Dental dams are latex or polyurethane sheets that are used as a barrier between the mouth and vagina, penis, or anus during oral sex. They are rectangles of about 10 inches by 6 inches and are available online and at some health clinics, specialty sex shops and drug stores without a prescription. You can also easily make a homemade dental dam.

## 1 Open Carefully

Unfold the dam and check for holes or damage that could make it less effective.

## 2 Placement of the Dental Dam

Put the dam flat across the vaginal or anal area before any oral contact. One partner needs to hold it in place.

## 3 Afterwards

Fold the dam up and throw it in the garbage and do not reuse it.

## Lubricants

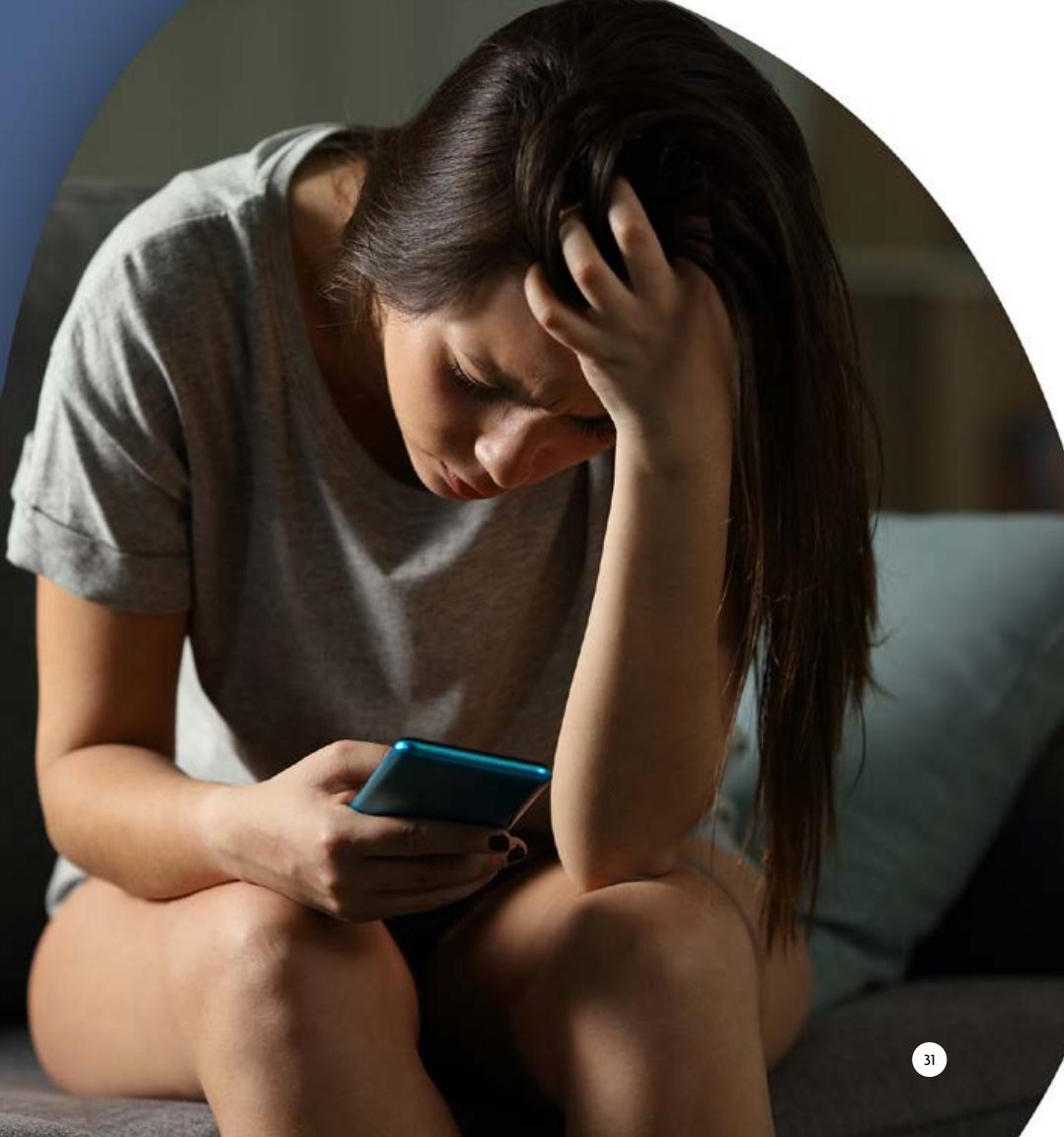
A water-based personal lubricant may be used directly on vaginal or anal areas before putting the dam in place and can help hold the dam in place.



### DIY

You can make a dental dam from an unlubricated condom by rolling it out, cutting off the top and the ring, and then cutting along the length to create a rectangle.

# **STI Symptoms and Treatments**



# Syphilis

## What is it?

Syphilis is a bacterial infection that is on the rise in Canada. If undetected, during the first two years of infection, you can pass on syphilis, even if you do not have any symptoms. After these two years, you will still have the infection, but you cannot pass it on. If syphilis is left untreated, it can cause serious health problems including damage to the brain, heart and other organs in the body, which can become permanent.

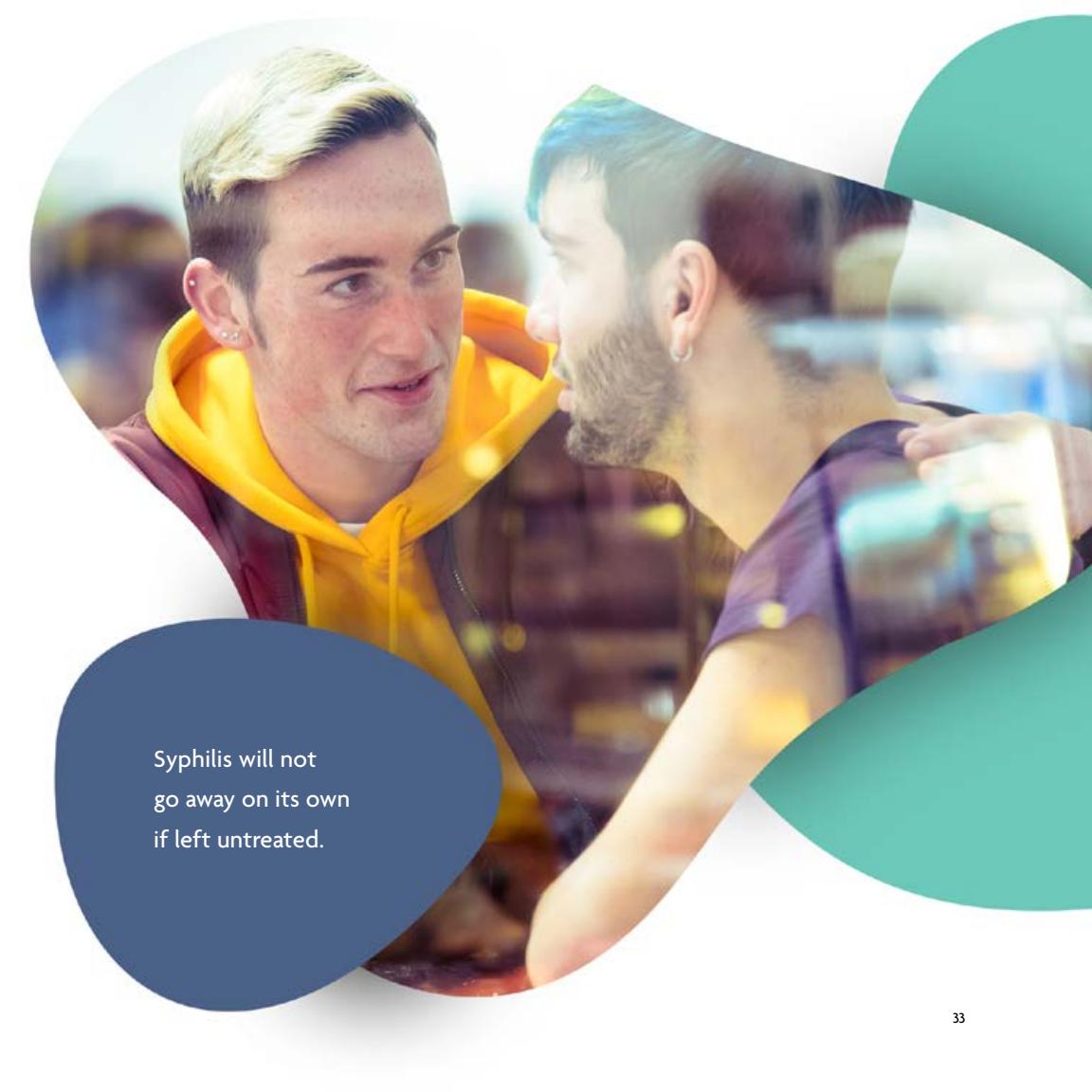
## How do you get it?

Syphilis is spread by having condomless vaginal, anal and/or oral sex with someone who has the infection.

Syphilis can be passed on to a baby during pregnancy or childbirth. Syphilis in babies can cause serious health problems or death. If you are pregnant, it is important to get tested and treated.

## The number of people with syphilis is increasing.

While it is more common among men, syphilis is increasingly affecting women.



Syphilis will not  
go away on its own  
if left untreated.

## How can you tell if you have it?

### Symptoms may include:

- An open sore that does not hurt, called a chancre, on the genitals, anus or throat. The sore will go away even if it is not treated, but you will still have syphilis.
- Some chancres might not be apparent since they are painless. A chancre in the vagina might go unnoticed.
- A body rash and/or feeling like you have the flu. These symptoms will also go away even if they are not treated.
- Swollen glands (lymph nodes) including behind the ears, under the jaw, in the armpits and in the groin. The swelling may feel like small bumps underneath the skin.

### IF YOU HAVE SYPHILIS

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You should notify your sexual partner(s) so that they can be tested and treated, if needed, and avoid exposing others. If you are uncomfortable notifying your partner(s), ask your healthcare provider or local public health unit for assistance.



### **How do you get tested?**

You get tested for syphilis with a blood test. You may also have a swab taken of your sore(s). Having a chancre can also increase your risk of getting or passing on HIV.

It is possible to have more than one infection at the same time. If you are tested for syphilis, have a discussion with your healthcare provider about which other STI testing should be done. Make sure to also ask about being tested for HIV, because it may not be part of routine STI testing.

### **How is it treated?**

Syphilis can be cured with antibiotics. Once you have been treated for syphilis, you will need to go for follow-up blood tests to make sure the infection is gone. It is important that you attend all of the scheduled visits.

# Gonorrhea

## What is it?

Gonorrhea is a bacterial infection that often occurs at the same time as chlamydia. Gonorrhea is on the rise in Canada and around the world and is becoming increasingly resistant to antibiotics.

That means that one day current antibiotics may not work to treat this infection.

If left untreated, gonorrhea can cause serious health problems including infertility, pelvic inflammatory disease, chronic pelvic pain, an increased risk of ectopic pregnancy (a pregnancy that occurs outside the uterus), and pain in the testicles.

## How do you get it?

You can get gonorrhea if you have condomless oral, vaginal and/or anal sex with someone who has an infection. If you are pregnant, it is important to get tested and treated for gonorrhea to avoid passing the infection on to the baby during childbirth.



## **How can you tell if you have it?**

You can pass on gonorrhea to someone without even knowing that you have it, as you may not have any symptoms.

## **If you have gonorrhea and you do have symptoms, you might notice:**

### **FOR PEOPLE WITH VAGINAS:**

- A change or an increase in discharge from the vagina
- Bleeding between periods
- Pain or bleeding during or after vaginal sex
- Pain in the lower abdomen
- Burning sensation while urinating

### **FOR PEOPLE WITH PENISES:**

- Burning sensation while urinating
- Discharge from the penis
- Burning or itching around the opening of the penis
- Pain in the testicles

## **How do you get tested?**

You get tested for gonorrhea with a urine sample. You may also have a swab taken from the throat, cervix, anus or penis. If you are tested for gonorrhea, have a discussion with your healthcare provider about which other STI testing should be done. It is possible to have more than one STI at the same time. Make sure to also ask about being tested for HIV, because it may not be part of routine STI testing.

The number of people with gonorrhea has

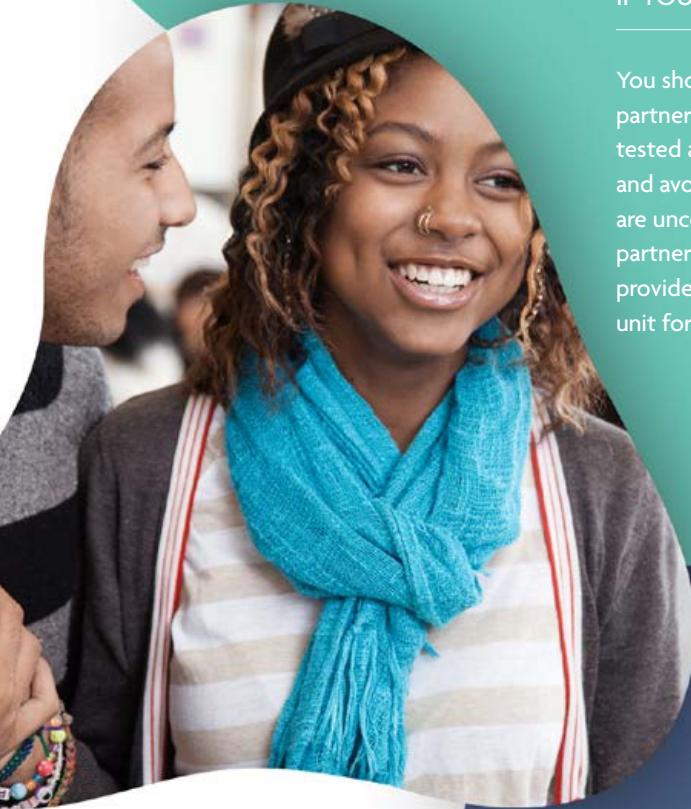
**doubled in the past 10 years**

with over 75 new cases reported in Canada every day.

## **How is it treated?**

It is becoming more and more difficult to treat gonorrhea with existing antibiotics. It is important that you take your medication as prescribed even if you start to feel better. If you have finished your treatment for gonorrhea and still have symptoms, you should go back to your healthcare provider as soon as possible because you may need additional treatment.

Many people who have gonorrhea also have chlamydia and are treated for both infections at the same time.



## IF YOU HAVE GONORRHEA

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You should notify your sexual partner(s) so that they can be tested and treated, if needed, and avoid exposing others. If you are uncomfortable notifying your partner(s), ask your healthcare provider or local public health unit for assistance.

# Chlamydia

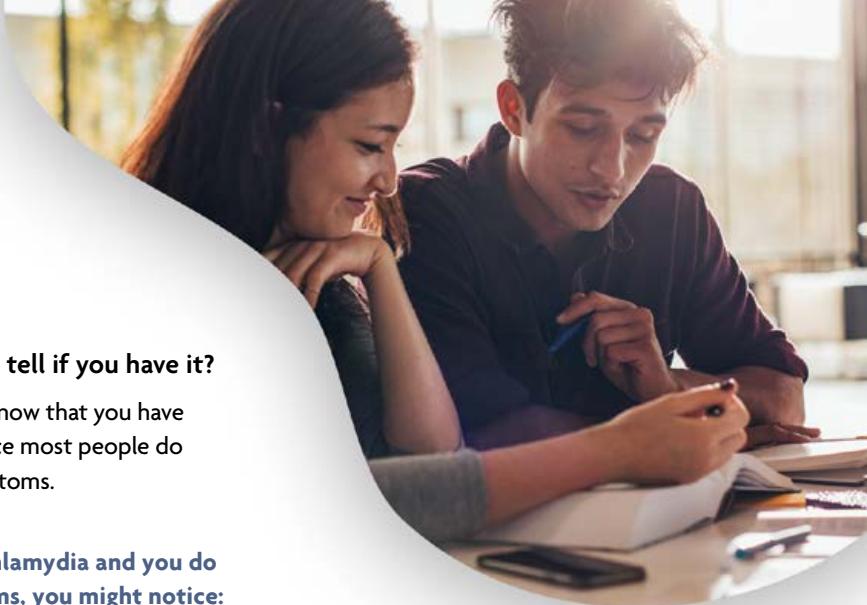
## What is it?

Chlamydia is a bacterial STI that is very common, especially in people aged 15–24. Most people who have chlamydia do not have any signs or symptoms. But if it is left untreated, chlamydia can cause serious health problems including infertility, pelvic inflammatory disease, chronic pelvic pain, and can increase the risk of ectopic pregnancy (a pregnancy that occurs outside the uterus).

## How do you get it?

You can get chlamydia if you have condomless oral, vaginal and/or anal sex with someone who has the infection. If you are pregnant, it is important to get tested and treated for chlamydia to avoid passing the infection on to the baby during childbirth.

*Certain STI such as chlamydia, gonorrhea and syphilis often have no symptoms at all. If you're getting tested for one, you should get tested for others. Make sure to also ask about being tested for HIV, because it may not be part of routine STI testing.*



## How can you tell if you have it?

You may not know that you have chlamydia, since most people do not have symptoms.

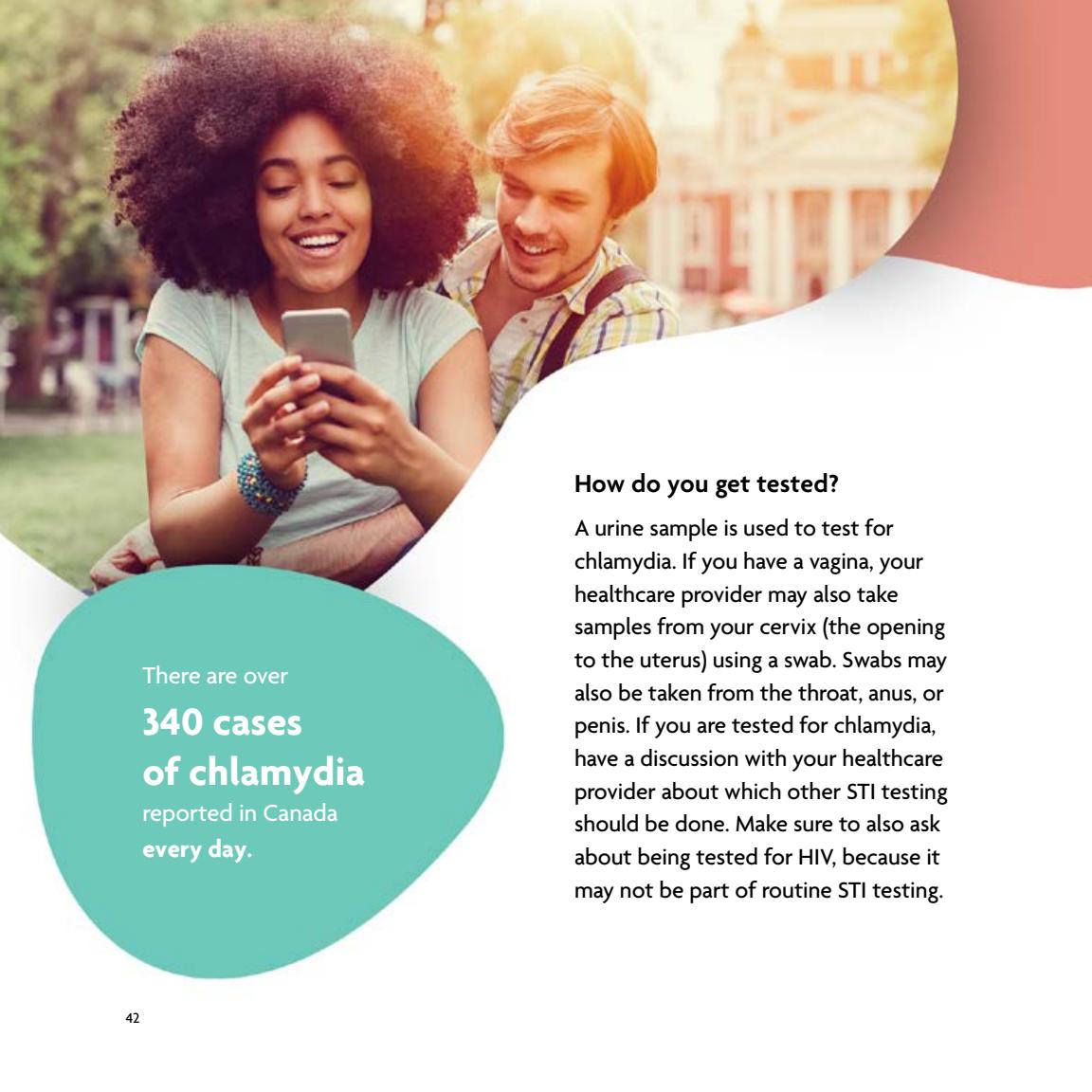
### If you have chlamydia and you do have symptoms, you might notice:

#### FOR PEOPLE WITH VAGINAS:

- A change or an increase in discharge from the vagina
- Vaginal itching
- Bleeding between periods
- Pain or bleeding during or after vaginal sex
- Pain in the lower abdomen
- Burning sensation while urinating

#### FOR PEOPLE WITH PENISES:

- Burning sensation while urinating
- Discharge from the penis
- Burning or itching around the opening of the penis
- Pain in the testicles



There are over  
**340 cases**  
**of chlamydia**  
reported in Canada  
every day.

### How do you get tested?

A urine sample is used to test for chlamydia. If you have a vagina, your healthcare provider may also take samples from your cervix (the opening to the uterus) using a swab. Swabs may also be taken from the throat, anus, or penis. If you are tested for chlamydia, have a discussion with your healthcare provider about which other STI testing should be done. Make sure to also ask about being tested for HIV, because it may not be part of routine STI testing.

## IF YOU HAVE CHLAMYDIA

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You should notify your sexual partner(s) so that they can be tested and treated, if needed, and avoid exposing others. The test and treatment are simple and can cure the infection. If you are uncomfortable notifying your partner(s), ask your healthcare provider or local public health unit for assistance.

### How is it treated?

Chlamydia can be cured with antibiotics. If you are prescribed antibiotics it is important that you take your medication as prescribed, even after you start to feel better. Even if you are treated for this infection, you can get it again if you have sex with someone who has the infection and has not been treated or has not finished treatment.

A different type of chlamydia can also cause a less common form of STI called lymphogranuloma venerum, also known as LGV or venereal disease. See page 44 for more information.

# Lymphogranuloma Venereum

## What is it?

Lymphogranuloma venereum (LGV) is an STI caused by a certain type of chlamydia bacteria. LGV can infect the:

- Vagina
- Penis
- Cervix (the opening to the uterus)
- Anus
- Mouth

LGV is relatively rare in Canada but cases have been reported, particularly among gay, bisexual and other men who have sex with men. Left untreated, LGV can cause serious health problems such as scarring and deformity to the genitals and rectum (the lower part of the large intestine) that may need surgery. LGV must be treated.

## How do you get it?

You can get LGV if you have condomless oral, vaginal and/or anal sex with a person who has the infection.

## How can you tell if you have it?

### There are usually three stages of LGV infection:

- 1 A painless sore or lump may appear where the bacteria entered your body. The sore may go away without treatment, but the infection is still there and needs to be treated. Having a sore can increase the risk of getting or passing on other infections such as HIV, hepatitis B or hepatitis C.
- 2 In the second stage you may develop swelling of the glands (lymph nodes), flu-like symptoms, discharge from the genital or anal area, and/or rectal pain and bleeding.
- 3 If left untreated, at this stage the symptoms can become more severe. You may be able to feel swollen glands behind the ears, under the jaw, in the armpits and in the groin. You may also experience swelling of the genitals or the rectum.



### **How do you get tested?**

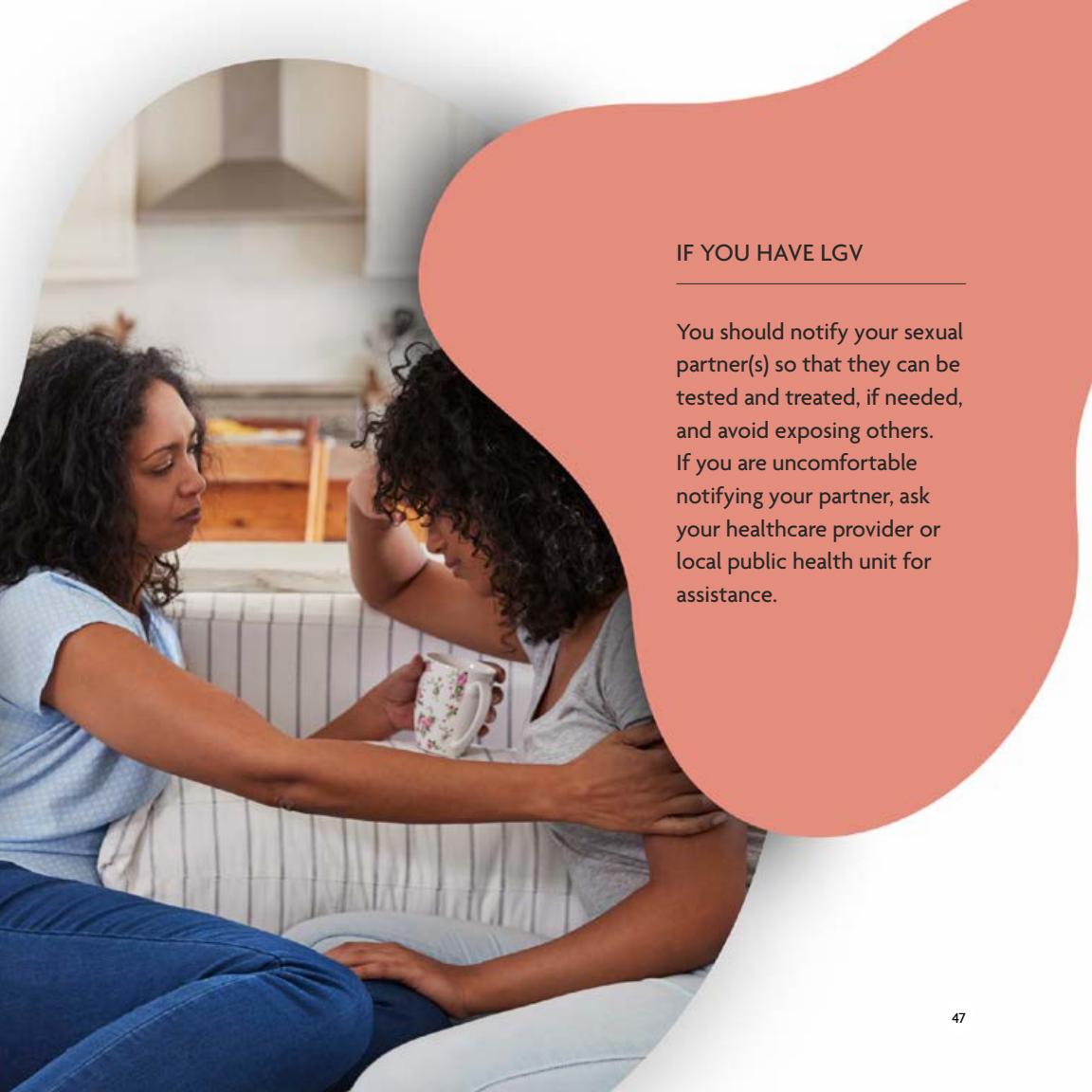
LGV is tested by taking samples from the sores using a swab or by doing a urine test. If your glands are swollen, your healthcare provider may also take a sample of liquid from your glands. If you are tested for LGV have a discussion with your healthcare provider about which other STI testing should be done.

### **How is it treated?**

LGV can be cured with antibiotics. It is important that you take all of your medication as directed by your healthcare provider, even if you start to feel better.



*Proper use of condoms  
and/or dental dams on  
a consistent basis can  
prevent LGV.*

A photograph showing two women in a kitchen. One woman, with dark curly hair and wearing a light blue shirt, is sitting on a white chair, looking down with a somber expression. The other woman, also with dark curly hair and wearing a grey tank top, is sitting next to her, holding a white mug with a floral pattern and placing her hand on the first woman's arm in a comforting gesture.

## IF YOU HAVE LGV

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You should notify your sexual partner(s) so that they can be tested and treated, if needed, and avoid exposing others. If you are uncomfortable notifying your partner, ask your healthcare provider or local public health unit for assistance.

# Human Immunodeficiency Virus (HIV)

## What is it?

Human Immunodeficiency Virus (HIV) is a virus that attacks the body's immune system. HIV may lead to acquired immune deficiency syndrome (AIDS) if it is left untreated.

Approximately  
**seven**  
**Canadians**

are newly diagnosed  
with HIV in Canada  
every day.



## **How do you get it?**

HIV is spread by having condomless vaginal, anal and/or oral sex with someone who has the infection, by coming in contact with infected blood or blood products, and by sharing needles or other drug equipment (syringes, cookers, water, filters, etc.) with someone who has HIV.

If you are pregnant or thinking about getting pregnant, get tested for HIV. If you are HIV positive, with proper treatment and care before and during pregnancy, you can have a healthy baby. In Canada, formula feeding is recommended to mothers who have HIV to prevent transmission to the baby.

HIV cannot be passed on through hugging, kissing or casual contact like shaking hands or giving someone a high-five or pat on the back.

If you are HIV-positive and being treated with antiretroviral medication that suppresses the virus to undetectable levels, there is effectively no risk of transmitting HIV sexually to your partner(s).

There are situations where taking pre-exposure prophylaxis (PrEP) can help to prevent you from getting HIV. Your healthcare provider can help you decide whether PrEP is appropriate for you. PrEP does not protect against other STI so be sure to use condoms to prevent transmission of other STI.

If you think you have been exposed to HIV through contact with blood, breast milk, vaginal or anal secretions, post-exposure prophylaxis (PEP) can reduce the risk of contracting HIV. PEP needs to be started within 72 hours of exposure for maximum effect and requires consultation with a healthcare provider.

Because HIV weakens the immune system, it can be easier for someone with HIV to contract other STI as well. Having an STI that causes sores, such as herpes or syphilis, increases the risk of getting HIV or passing HIV to a partner.

If you have HIV, the best way to protect yourself and your partner is to take your medication to achieve and maintain an undetectable viral load and to use condoms consistently for protection against other STI.



*Proper use of condoms and/or dental dams on a consistent basis can prevent HIV. You can also use PrEP to prevent the transmission of HIV if you are more likely to be exposed to HIV.*

### **How can you tell if you have it?**

Some people present no symptoms for many years, whereas other people may develop mild flu-like symptoms two to four weeks after contracting HIV.

**Common early symptoms can include:**

- Fever
- Sore throat
- Headache
- Muscle aches and joint pain
- Swollen glands (lymph nodes)

## How do you get tested?

HIV is diagnosed using a blood test.

HIV will show up in a blood test approximately three to four weeks after you have contracted the infection, so it is important to be retested if the window between testing and exposure to HIV is really short.

However, if you know you have been exposed to HIV, you can seek medical attention prior to a blood test. A health care professional may recommend you start post-exposure prophylaxis (PEP) medication immediately.

If you are tested for HIV, have a discussion with your healthcare provider about which other STI testing should be done. It is possible to have more than one infection at the same time. This requires specialized treatment and care.

It is important that you follow up for your test results and any treatment you might need.



## **How is it treated?**

There is no cure for HIV, but it can be managed with antiretroviral medications and medical supervision.

Antiretroviral medications help lower the amount of virus in your body, keep your immune system healthy, and, in this way, help you fight off other infections.

If you are HIV-positive, you can live a longer and healthier life if you start treatment early. You can also prevent sexual transmission of HIV to your partner if you are on treatment and have an undetectable viral load.

## **IF YOU ARE DIAGNOSED WITH HIV**

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You must notify your sexual partner(s) so that they can be tested and treated. If you are uncomfortable notifying your partner(s), ask your healthcare provider or local public health unit for assistance. Resources are available at [CATIE.ca](http://CATIE.ca) if you have questions about your obligations to disclose your status.

# Hepatitis B

## What is it?

Hepatitis B is a virus that can infect the liver and sometimes leads to severe liver damage or cancer of the liver.

## How do you get it?

Hepatitis B is spread by having condomless vaginal, anal and/or oral sex with a person who has the infection. It can also be spread through sharing contaminated drug-use equipment (e.g.: needles, straws, pipes, cookers, etc.) to inject or snort drugs; tattooing, body piercing or acupuncture when unsterile equipment is used; unsterilized medical

equipment; and, through blood or cutting rituals. While less common, it can also be spread by sharing personal care items like a razor, nail clippers or a toothbrush with a person who has the infection.

## Prevention

You can protect yourself against hepatitis B by getting the hepatitis B vaccine. If you did not receive the vaccine as a child or are unsure, you can still get it as an adult. If you have hepatitis B, your sexual partner(s) should be vaccinated.



*If you are pregnant, you can pass hepatitis B to the baby during childbirth, so it is important to get tested. Let your healthcare provider know if you have hepatitis B.*

## **How can you tell if you have it?**

You may not have any signs or symptoms, so you can pass the virus on without knowing that you have it.

### **If you do have symptoms, they may include:**

- Tiredness
- Pain in the abdomen
- Dark urine and/or pale stools
- Lack of appetite
- Nausea
- Yellowing of the skin and/or the whites of the eyes (jaundice)

## **How do you get tested?**

You get tested for hepatitis B using a blood test. If you are tested for hepatitis B, have a discussion with your healthcare provider about which other STI testing should be done. It is possible to have more than one infection at the same time. This requires specialized treatment and care.

### **IF YOU HAVE HEPATITIS B**

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You should notify your sexual partner(s) and household members so that they can get vaccinated to protect themselves. If you are uncomfortable notifying your partner(s), ask your healthcare provider or local public health unit for assistance.

## **How is it treated?**

In most people, the virus will go away on its own within six months, but it can be passed on to others during this time. Once the body fights off the infection, you are protected from ever getting the virus again and cannot pass it on to others.

If you think you have been exposed to hepatitis B your healthcare provider may inject you with an antibody (immune globulin) within 12 hours of exposure to the virus. For longer-term protection, you should get the hepatitis B vaccine at the same time.

There are some cases where other treatments like antivirals may be recommended.

Some people will not respond to treatment and will have hepatitis B for life. As long as they have the virus they can pass it onto others.



# Hepatitis C

## What is it?

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). Hepatitis C can lead to severe liver damage and cancer of the liver. There is no vaccine to prevent it.

## How do you get it?

Hepatitis C is spread through contact with infected blood. It is most often spread through sharing contaminated drug-use equipment (e.g.: needles, straws, pipes, cookers, etc.) to inject or snort drugs; tattooing, body piercing or acupuncture when unsterile equipment is used; unsterilized medical equipment; and, through blood or cutting rituals. It can also be spread by sharing personal care items like a razor, nail clippers or a toothbrush with a person who has the infection.

Sexual transmission of hepatitis C is less common, but it can be transmitted sexually, especially when there is a chance that infected blood is present (such as during menstruation).



## How can you tell if you have it?

The majority of people will not develop symptoms and will not know they have the virus. If symptoms do develop it can take two to six months for them to appear. People can pass the virus on without even knowing that they have it.

### If you do have symptoms, they may include:

- Tiredness
- Pain in the abdomen
- Dark urine and/or pale stools
- Lack of appetite
- Nausea
- Yellowing of the skin and/or the whites of the eyes (jaundice)

*Hepatitis C can be passed on to the baby during pregnancy or childbirth, so it is important to tell your healthcare provider if you have hepatitis C or ask if you should be tested.*

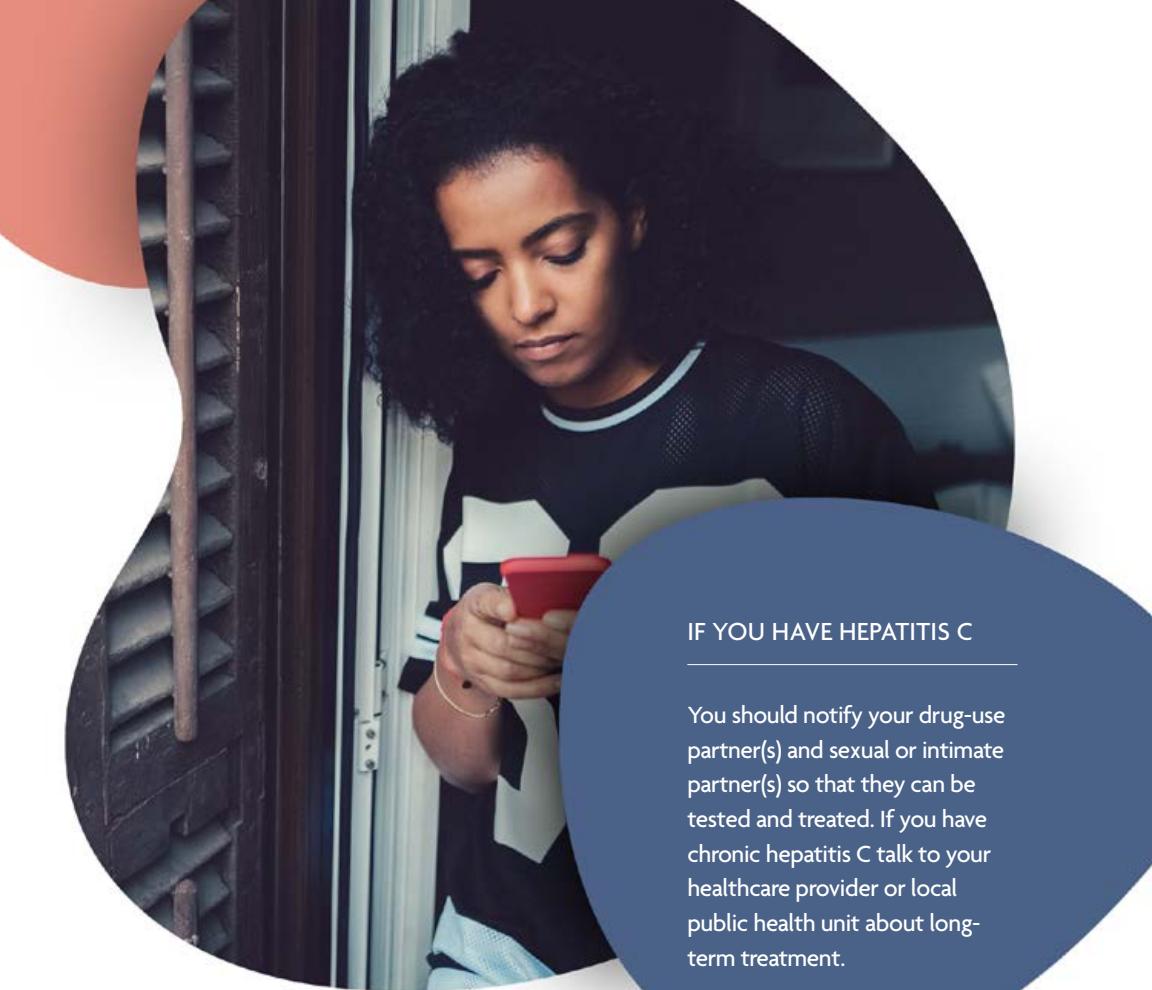
## **How do you get tested?**

A blood test can tell if you have hepatitis C. If you are tested for hepatitis C, have a discussion with your healthcare provider about which other STI testing should be done. It is possible to have more than one blood-borne infection at the same time. This requires specialized treatment and care.

## **How is it treated?**

Some adults with hepatitis C will clear the virus on their own within six months. There are several drug combinations that have been approved by Health Canada to treat hepatitis C and to prevent progression of liver disease caused by hepatitis C.

Even if you clear the virus on your own or with treatment, you can still contract it again. Many people with hepatitis C develop a long-term infection called chronic hepatitis C, which can lead to severe liver damage and liver cancer. Chronic hepatitis C is treatable and can almost always be cured.



### IF YOU HAVE HEPATITIS C

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You should notify your drug-use partner(s) and sexual or intimate partner(s) so that they can be tested and treated. If you have chronic hepatitis C talk to your healthcare provider or local public health unit about long-term treatment.

# **Human Papillomavirus (HPV)**

## **What is it?**

HPV is short for Human papillomavirus. There are about 200 types of HPV that can infect different parts of the body.

Some types of HPV can:

- Cause warts on the penis, scrotum and thighs.
- Cause warts on the inside or outside the vagina, anus or throat.
- Cause cell changes that can lead to cervical, oral or anal cancers.

You can have more than one type of HPV at a time.

## **How do you get it?**

You can get HPV if you have condomless oral, vaginal and/or anal sex with a person who has the virus.

You can also get HPV from other sexual activity involving intimate skin-to-skin contact. You or your partner(s) can still spread the virus even if you do not have any symptoms.

## **Vaccination is up**

## **to 90% effective**

at preventing the HPV types responsible for most genital warts and HPV-related cancers.

## **How can you tell if you have it?**

Most people do not have symptoms. This is why it is so hard to detect. Depending on the type of HPV you have, you may get warts on your genitals or anus which may look like bumps that can be cauliflower-like or may look like flat white patches. Some warts are very hard to see so you may feel them before you see them. Sometimes HPV doesn't cause visible warts, but rather abnormalities on Pap tests. Pap tests involve collecting cells from the cervix during an appointment with a healthcare provider, and examining them under a microscope to make sure the cells are healthy.



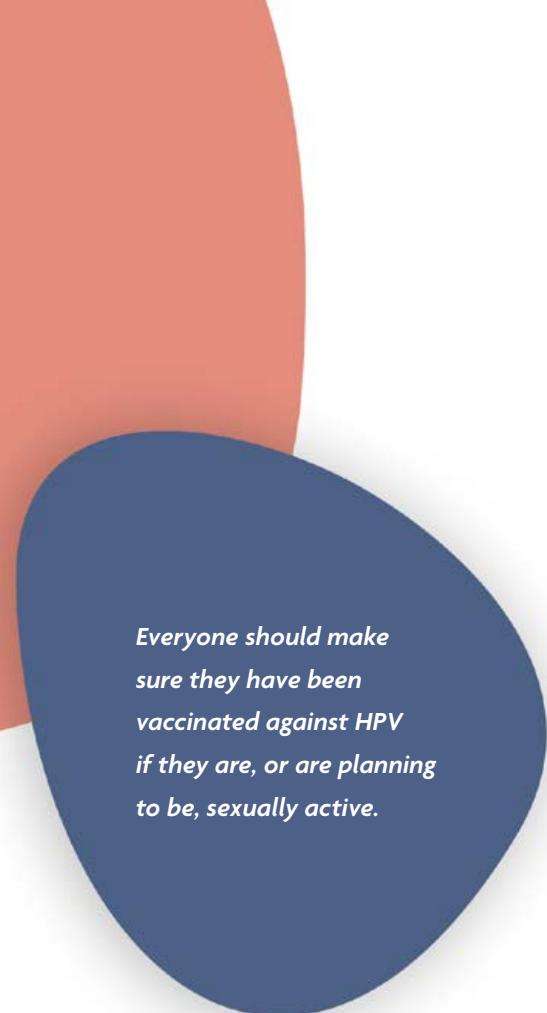
## **HPV Vaccine**

Youth aged 9–26 should get their HPV vaccine, but it might also be appropriate for adults older than 26 years of age. Ideally, you should get the vaccine before becoming sexually active and exposed to HPV.

If you are sexually active, you can still benefit from HPV vaccination. Few sexually active people have contracted all types of HPV that are prevented by the vaccine, so you will still get protection by getting the vaccine.

The vaccine is not recommended during pregnancy.

Vaccine schedules can vary across provinces and territories. For information on how to get the vaccine where you live, speak to your healthcare provider or local public health unit.



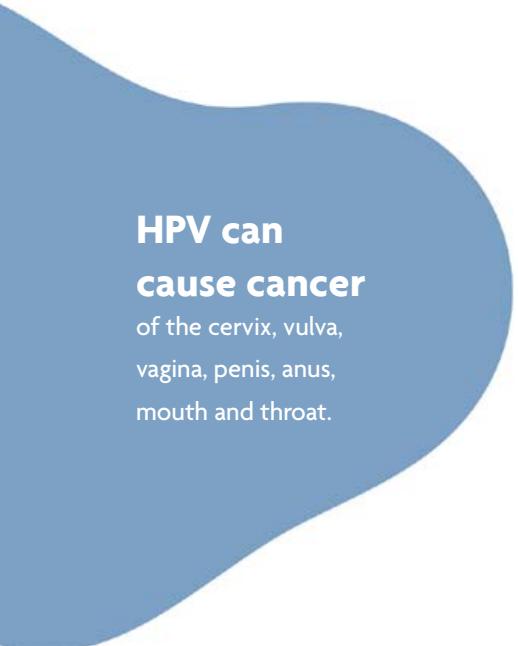
***Everyone should make  
sure they have been  
vaccinated against HPV  
if they are, or are planning  
to be, sexually active.***

## **How do you get tested?**

A healthcare provider can usually tell if you have oral or genital warts by doing a visual exam. Regular cervical cancer screening (Pap/HPV test) is important for all people with a cervix who are, or have ever been, sexually active. The cervix is located in the lower, narrow end of the uterus at the end of the vagina. The screening tests can detect abnormal cell changes in the cervix that may cause cancer.

Pap test screening usually begins at age 21 and is repeated periodically after that. There is currently no test to detect high-risk HPV in people with penises.

If you are tested for HPV, have a discussion with your healthcare provider about which other STI testing should be done. The need for additional testing depends on risk factors and should be assessed by a healthcare provider.



**HPV can  
cause cancer**  
of the cervix, vulva,  
vagina, penis, anus,  
mouth and throat.

### **How is it treated?**

HPV cannot be cured, but oral or genital warts caused by HPV will often go away without treatment. Your healthcare provider can advise you on how to treat them if they do not go away on their own. Some ways that oral or genital warts can be removed include:

- Freezing the warts with a very cold liquid called liquid nitrogen.
- Applying an ointment or liquid to destroy the warts.
- In some cases a surgical procedure may be required.

Treatment does not prevent re-infection or recurrence of HPV. You can still get another HPV infection in the future.



*HPV vaccination is the best way to prevent genital warts and cervical cancer. Condoms will reduce the risk of transmission but are not 100% effective, because HPV can live in areas not covered by condoms.*

# Genital Herpes

## What is it?

Genital herpes is an infection caused by the herpes simplex virus (HSV). The HSV type 1 causes sores around the mouth called “cold sores” and it can also cause sores on the genitals. HSV type 2 usually causes genital herpes.

**500 million  
people worldwide**

are estimated to have the herpes simplex virus genital infection.

## How do you get it?

Genital herpes is generally passed on through condomless oral, vaginal and/or anal sex with a partner who has the infection, whether the person has sores or not.

You can spread herpes to other parts of your or your partner’s body by touching the sores or fluids from the sores and then touching elsewhere, for example, your eyes, mouth or genitals.



### How can you tell if you have it?

Many people who have herpes will not have symptoms and may not know they have it. When you first have an outbreak of herpes, there may be itchiness along with very painful sores and blisters. The sores usually go away on their own, but you will still have the virus. An outbreak may also include painful swollen glands in the groin and flu-like symptoms. These symptoms may last several weeks.

*If you are pregnant, you can pass the virus on to your baby during pregnancy or childbirth. Tell your healthcare provider if you have herpes. They can give you medications to reduce the risk of your baby getting herpes.*

## **Can it keep coming back?**

Herpes can keep coming back. These are called recurrences. There is no way to predict if or how often recurrences will happen. Your healthcare provider can give you information on how to manage the infection, including treatment to control recurrences. Some common causes of recurrences include:

- Fatigue and stress
- Existing illness
- Overexposure to sun
- Your period
- Pregnancy

## **How can you prevent passing on the virus?**

- If you feel a burning or tingling sensation but have no sores, do not have sex. This is a sign that you may be developing an outbreak and even without the sores, you can pass on the virus.
- You should avoid oral sex when you have a cold sore.
- You should not have sex if you have an outbreak of genital herpes. Wait until several days after the sores are completely healed.
- Proper and consistent use of condoms and/or dental dams can lower your risk of passing on or getting the virus because herpes can be passed even when there aren't any symptoms.



### **How do you get tested?**

Genital herpes is most often tested by taking a swab from a herpes sore. If you do not have sores when you visit your healthcare provider, you may have to delay testing. If you are tested for genital herpes, have a discussion with your healthcare provider about which other STI testing should be done.

## **What can you do if you have a genital herpes outbreak?**

- Keep the area clean and dry.
- Avoid using ointments and creams, which can cause the infection to spread.
- Wear cotton underwear.
- Wear loose fitting clothes.
- After urinating, avoid wiping the area. Pat it dry to avoid spreading the infection.
- If it hurts when you urinate, sit in a tub of warm water or pour warm water over the area while you are urinating.



### **How is it treated?**

Genital herpes cannot be cured but it can be managed. There are medications that may help to prevent outbreaks or reduce how long the outbreak lasts. Your healthcare provider may also prescribe medication for pain if your outbreaks are severe and cause discomfort.

### **How is it prevented?**

Since many people with herpes do not have any symptoms, proper use of condoms and/or dental dams on a consistent basis can help prevent herpes, but is not 100% effective as herpes can be present in areas not covered by condoms.

### **IF YOU HAVE HERPES**

---

You should notify your sexual partner(s) so that they can practise safer sex with you. If they have contracted the virus, they can be treated, and avoid passing it on to others. If they do not have herpes, they can choose to use condoms and avoid sex during outbreaks, to lessen but not eliminate their chance of contraction. If you are uncomfortable notifying your partner(s), ask your healthcare provider or local public health unit for assistance.

# Pubic Lice and Scabies

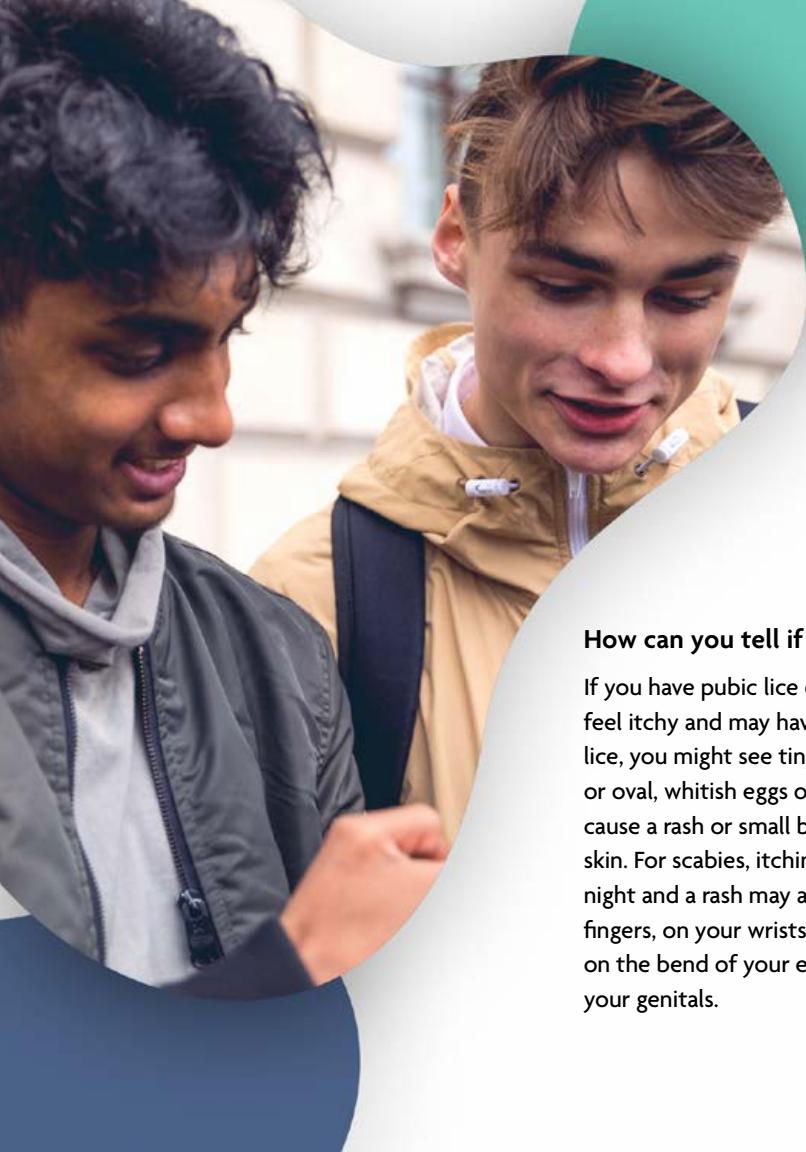
## What is it?

Pubic lice are also known as “crabs” because the lice resemble tiny crabs. They are usually found around the genitals in the pubic hair. You can get pubic lice from having close contact with someone who has it. Lice can be clear to darker brown in colour. They live by feeding on human blood and lay their eggs at the base of the pubic hair. Their eggs are called nits and can stay alive for up to 10 days.

Scabies are tiny bugs or mites that burrow below the surface of the skin and lay eggs. They are not visible to the naked eye.

## How do you get it?

Pubic lice and scabies are passed on from one person to another through sexual and non-sexual contact. An example of non-sexual contact is sharing towels or sheets with a person who has pubic lice or scabies. Pubic lice and scabies can live on objects such as clothing, towels, bedding and mattresses for one to two days if they fall off their host.



### **How can you tell if you have it?**

If you have pubic lice or scabies you will feel itchy and may have a rash. For pubic lice, you might see tiny light brown insects or oval, whitish eggs on the hair. Bites can cause a rash or small bluish spots on your skin. For scabies, itching occurs mainly at night and a rash may appear between your fingers, on your wrists, abdomen, ankles, on the bend of your elbows or around your genitals.



## How do you get tested?

You can usually tell if you have pubic lice by finding the adult lice or eggs on the hair. If you are not sure if you have pubic lice or scabies, see your healthcare provider. If you have scabies or pubic lice you should discuss with your healthcare provider which other STI testing should be done.



The best way to protect against STI is to not have sex. If you are having any type of sex, the best way to protect yourself against STI is to use condoms and/or dental dams consistently and correctly.



## How is it treated?

Pubic lice and scabies are treated with special creams, lotions or shampoos available at the drug store without a prescription. The pharmacist can help you find the right product. You need to follow the directions carefully. Your partners, friends and family may also have lice or scabies and have to be treated too. Infants, those who are pregnant and those who are breastfeeding need a different treatment. Speak to a pharmacist to make sure that you use the safest treatment for you.

Because lice and scabies can live on clothing, towels, bedding and mattresses, you need to:

- Dry clean or machine wash all of your clothing in hot water.
- Wash all bed linen in hot water.
- Store quilts and blankets for one week in sealed airtight plastic bags if you cannot wash them.
- Vacuum everything that has been in contact that you cannot wash (mattress, carpets, etc.).

# Trichomoniasis

## What is it?

Trichomoniasis is caused by a parasite and must be treated. If you are pregnant and have trichomoniasis, your baby may be born early or be underweight at birth. You can also pass the infection on to your baby during childbirth.

## How do you get it?

Trichomoniasis is most often spread by having condomless vaginal sex with someone who has the infection.



**10–50%**  
**of people**  
of people who have  
trichomoniasis  
have no symptoms.

## **How can you tell if you have it?**

The infection is most commonly found in the vagina and the opening of the penis (urethra), but most people do not have symptoms. You can pass it on without knowing that you have it.

### **If you do have symptoms, they may include:**

- A change or increase in vaginal discharge
- Vaginal itching
- Pain during vaginal sex
- Burning during urination
- Discharge from the penis
- Burning or itching around the opening of the penis



If left untreated or if treatment is not completed,

## **STI can recur and spread to sexual partners as well.**

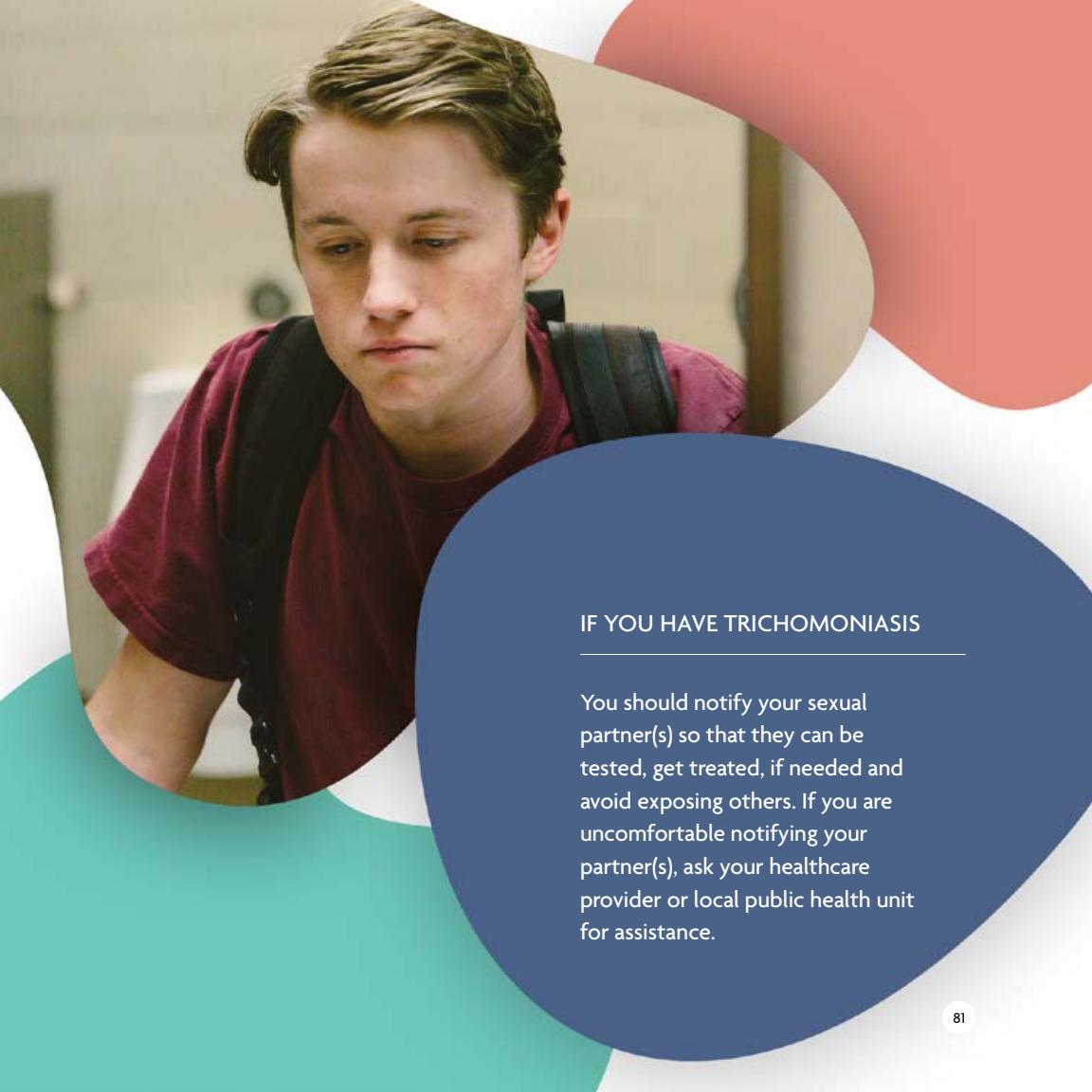
### **How do you get tested?**

You get tested for trichomoniasis by taking a swab of discharge from the vagina or from the tip of the penis. Trichomoniasis can also increase the risk of getting and passing on HIV.

It is possible to have more than one infection at the same time. If you are tested for trichomoniasis, have a discussion with your healthcare provider about which other STI testing should be done.

### **How is it treated?**

Trichomoniasis can be cured with antibiotics. It is important that you take your medication as prescribed, even if you start to feel better. You should not have sex until you have completed treatment. You can get the infection again if you have sex with someone who has trichomoniasis and has not been treated.



#### IF YOU HAVE TRICHOMONIASIS

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You should notify your sexual partner(s) so that they can be tested, get treated, if needed and avoid exposing others. If you are uncomfortable notifying your partner(s), ask your healthcare provider or local public health unit for assistance.

## Other, less common STI

### Mycoplasma genitalium

*Mycoplasma genitalium* is a bacterial infection that is passed through sex and genital contact and can be responsible for inflammation of the urethra (the tube that carries urine from your bladder to the outside), inflammation of the cervix, pelvic inflammatory disease and even infertility.

Usually a urine sample or swab is taken to test for mycoplasma genitalium if inflammation is detected. The best current treatment is with antibiotics, but mycoplasma genitalium is developing a resistance to some of these drugs, meaning you might need a combination of antibiotics.

It is important that you take your medication as prescribed even if you start to feel better. If you have finished your treatment for mycoplasma genitalium and still have symptoms, you should go back to your healthcare provider as soon as possible.

Re-testing may be necessary to determine whether the infection is gone, or if you need additional or alternate treatment.



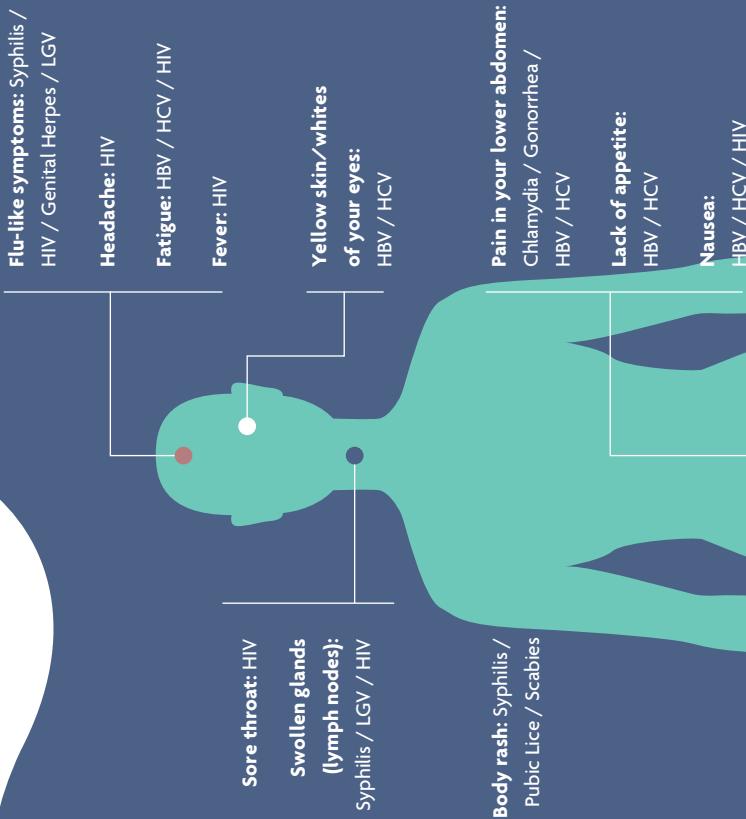
## **Molluscum contagiosum**

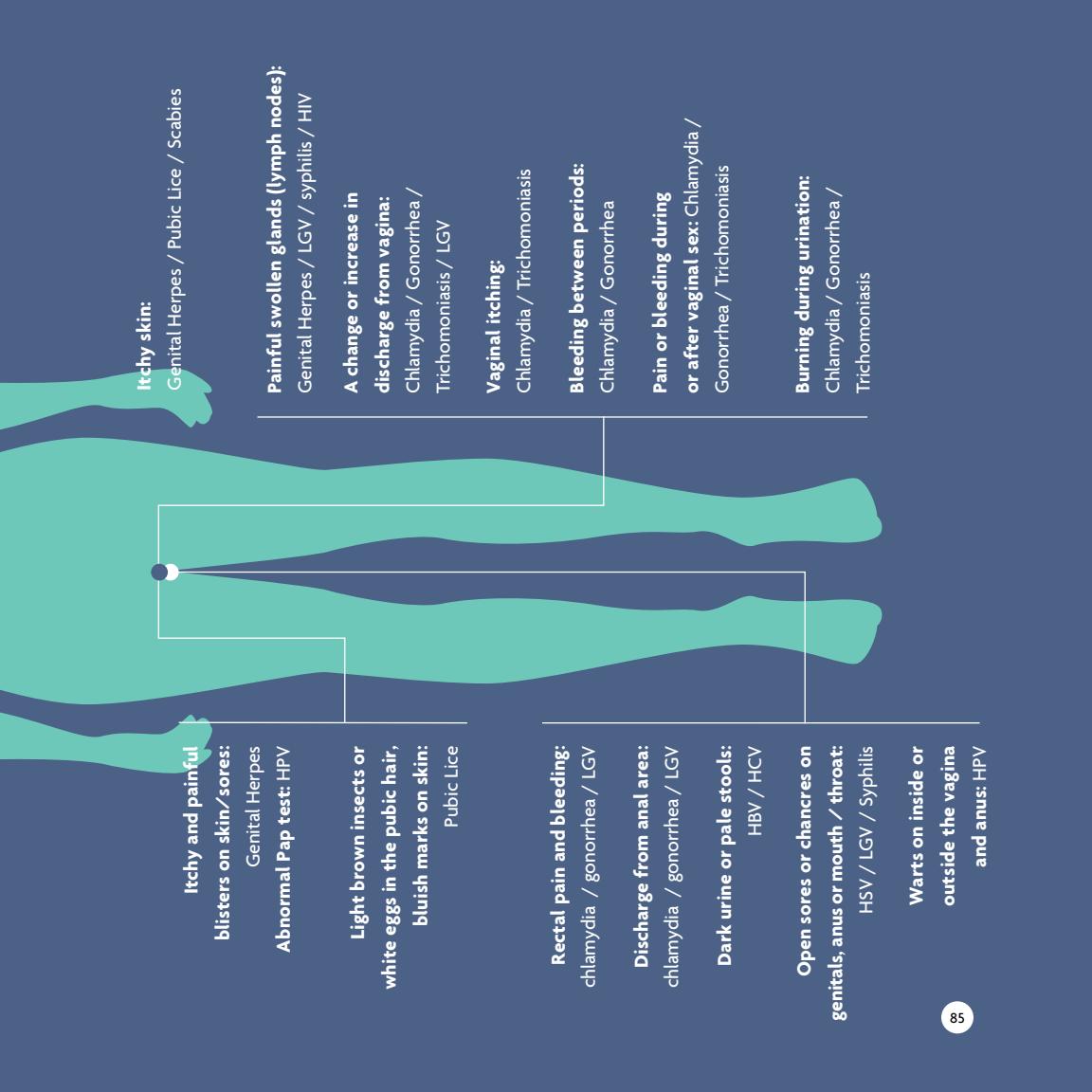
*Molluscum contagiosum* is a skin rash that is transmitted during oral, anal and/or vaginal sex, or from towels or clothing from someone who has the infection.

The rash can appear on the genitals, or eyes, nose and mouth, and will often go away without treatment, although it can cause scarring.

## SYMPTOM MAP for People with Vaginas

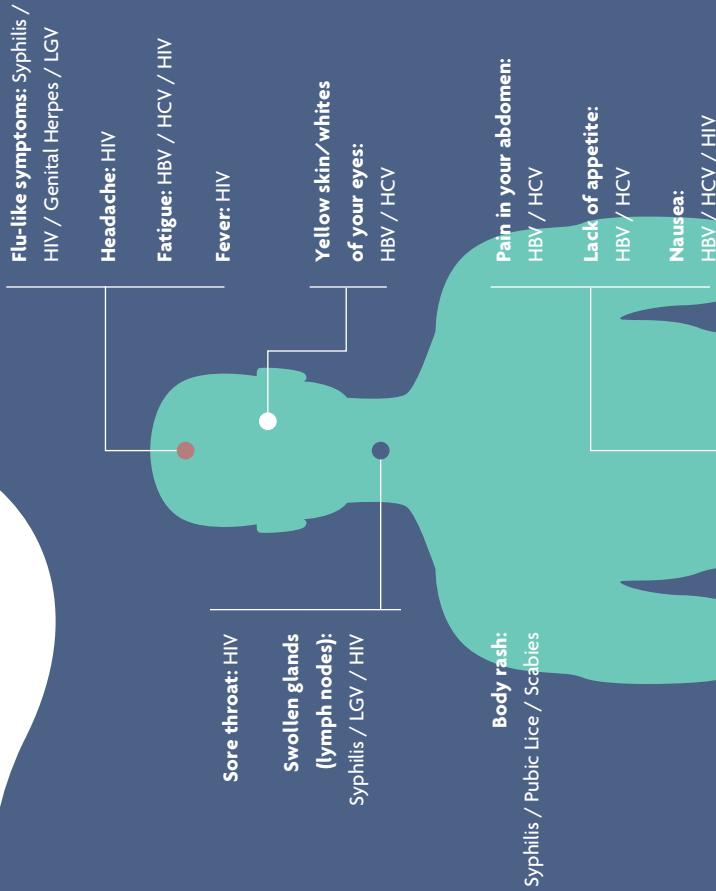
It's important to remember that many STI often have no symptoms. Get tested regularly and before each new sexual partner.

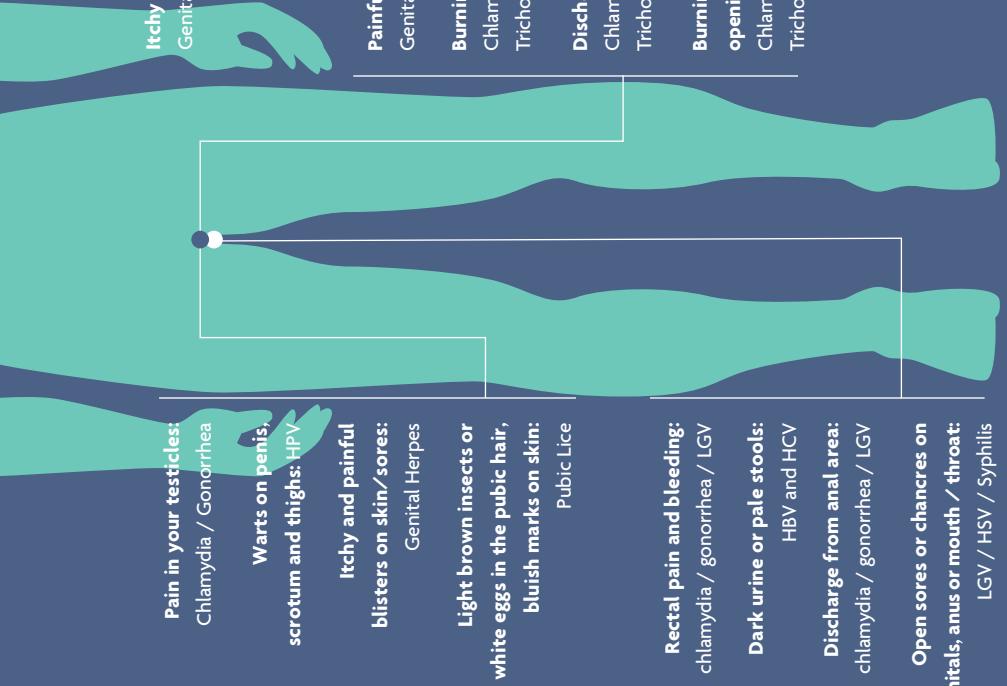




## SYMPTOM MAP for People with Penises

It's important to remember that many STI often have no symptoms. Get tested regularly and before each new sexual partner.





A close-up photograph of a person's hand wearing a white medical glove. The hand is holding a clear test tube with a dark liquid inside. In the background, a portion of a white lab coat is visible.

# Get Tested



## When should I go and get tested?

- If you or your partner have been sexually active with other people, both of you should get tested before you have sex together.
- If your partner is having sex with another partner.
- If you know your current or past partner has or had an STI.
- If the condom breaks or you have sex without one.
- If you or your partner have shared needles for drugs, tattooing or piercing, even once.
- If you or your partner have any STI symptoms.

*If you and your partner both get tested and do not have STI, you are only protected as long as you remain in a relationship with this same partner. When in doubt, talk to your partner about safer sex, testing, and use a condom and/or dental dam.*





## What do I need to know about the testing process?

No matter your sex assigned at birth, gender identity, expression, or sexual orientation, if you feel more comfortable with someone else in the room during your examination, tell your healthcare provider. Everything you discuss with your healthcare provider is confidential.

They cannot discuss things with anyone unless they:

- Have your permission.
- Are making a referral that you have agreed to.
- Are concerned you may not understand medical advice given or the consequences of your decisions.
- Suspect child abuse which they are required to report to a child protection agency.



*Positive test results for chlamydia, gonorrhea, syphilis, hepatitis B, hepatitis C and HIV are reported to your local public health department. However, your personal information is not given out to the health department or anyone else, and no one will know you have the infection except you, your healthcare provider and public health nurse. A nurse may contact you to offer to help with telling your current and past partners that they need to be tested.*

## What should I expect during my appointment?

The healthcare provider will ask you many questions about your sexual activity. They may ask you to undress from the waist down and will give you a drape to cover yourself. They may do some or all of the following:

- Ask for a urine sample.
- Take a blood sample.
- Use a cotton swab to take samples from the throat, cervix, anus, and/or urethra (the opening of the penis).
- Check the external parts of your genitals including testicles and penis for lumps or pain.

- Use a speculum to look at the inside of the vagina and at the cervix (the opening to the uterus).
- If you are 21 or older, they may do cervical cancer screening, including a Pap test, to check for changes in the cells of the cervix.
- Do a bimanual exam (the healthcare provider places one or two fingers inside the vagina and their other hand on the lower abdomen in order to feel the ovaries and uterus).

## How do I tell my partner(s) I have an STI?

If you have an STI, it is important that your sexual partner(s) be tested as well to make sure the infection does not spread further. There are many ways to tell your partner(s) that they need to get tested for STI.

There are programs and tools to help you tell your partner(s) anonymously that they need to get tested.

Contact your local public health department for more information.



## Quick facts on safer sex

- Educate yourself and know the risks— all kinds of sex, including oral, vaginal and anal intercourse, and intimate skin to skin contact can transmit infections through body fluids like blood, semen, vaginal secretions and saliva, as well as through bacteria.
- You and/or your sexual partner may not know that either of you have an STI and won't know that you may be spreading it.
- Always use condoms and/or dental dams during vaginal, anal or oral sex.
- If you haven't already, get vaccinated for HPV and hepatitis B.
- Get tested for STI regularly and before each new sexual partner. Request that your partner(s) do the same.

- Remember that you can get some STI by just touching or kissing an infected area.
- Be aware of your situation—you may take unnecessary risks when impaired by drugs or alcohol—always have a condom or dental dam accessible in case you are ‘caught up in the moment’.
- If you use recreational drugs, or get tattoos, be sure that the needles are sterile and haven’t been used by anyone else already.

A large, semi-transparent orange speech bubble is positioned in the upper left corner of the image. Inside the bubble, the text is written in a bold, italicized, black font.

**You matter.**  
**Your choices matter.**  
**You decide what is**  
**right for you.**



## Websites to visit

[SexandU.ca](#)

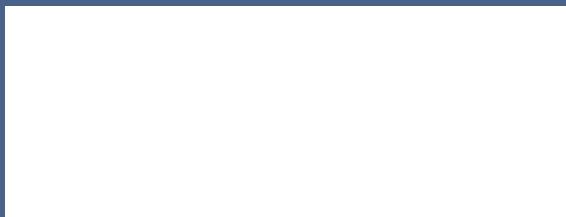
[catie.ca/en/home](#)

[canada.ca/en/public-health/services/sexual-health.html](#)

[canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections.html](#)

## **Where to go for help**

If you have questions or want to be tested for STI, you can go to your healthcare provider, clinics offering anonymous testing, sexual health clinic or local public health unit.



# REPORT ON SEXUALLY TRANSMITTED INFECTIONS IN CANADA, 2018



PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

**TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP,  
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—Public Health Agency of Canada

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The publication of this report would not have been possible without the collaboration of the provincial / territorial public health authorities, whose continuous contribution to national STI surveillance is gratefully appreciated.

## 1.0 Key Messages

- While sexually transmitted infections (STIs) are curable or manageable and prevention can reduce transmission, rates of STIs have been increasing dramatically over the last decade and continue to be a significant and increasing public health concern in Canada.
- In 2018, a total of 117,008 cases of chlamydia were reported as well as 30,874 cases of gonorrhea and 6,281 cases of infectious syphilis, which corresponded to rates of 363.2, 95.8 and 16.9 cases per 100,000 population, respectively.
- In 2018, more than three quarters (76.1%) of reported chlamydia cases were among people less than 30 years of age. This is similar (56.3%) to what is seen in gonorrhea, but in contrast to infectious syphilis, in which the same age groups accounted for only 37.8%.
- Gonorrhea rates have almost doubled in the past 5 years.
- Infectious syphilis rates have more than tripled in the past decade and experienced the highest increase in rates of all STIs with a more than 259.5% increase over this time period. Although the rate of reported syphilis cases among males was more than three times higher than that among females in 2018, in the past 5 years, females rates increased by 691.5%, compared to a 109.1% relative increase among males.

## 2.0 Introduction

Sexually transmitted infections (STIs) continue to be a significant and ever-increasing public health concern in Canada. STIs are among the most common communicable infections affecting the health and lives of people worldwide. Sexually transmitted pathogens have the ability to compromise the quality of life, as well as sexual and reproductive health, and newborn health<sup>1</sup>. STIs can also indirectly expedite the sexual transmission of human immunodeficiency virus (HIV) and can cause cellular changes that may precede some cancers<sup>1,2</sup>. Rates of notifiable STIs have increased despite numerous public health interventions designed to strengthen awareness and to prevent, diagnose and treat infection. There are various potential factors that may explain these observations such as true rise in incidence, the use of improved diagnostic methods, and more effective contact tracing and case finding<sup>2</sup>.

To address the STI epidemic, the World Health Organization, in 2016, published the *Global Health Sector Strategy on Sexually Transmitted Infections, 2016-2021: Towards Ending STIs*<sup>1</sup>. Supporting the goals and targets of this global strategy, the Government of Canada, in June 2018, released the *Pan-Canadian Sexually Transmitted and Blood-Borne Infection Framework for Action*<sup>3</sup>.

In July 2019, in response to the Framework, the Government of Canada launched its action plan – *Accelerating our Response: Government of Canada Five-Year Action Plan on Sexually Transmitted and Blood-Borne Infections*<sup>4</sup>, which emphasizes the tangible actions to be undertaken over the next five years to move Canada closer to achieving the strategic goals outlined in the Framework. Included is the development of Canadian-made targets and indicators, which will drive our domestic actions and unify us in our commitment to specific results<sup>4</sup>. Given the importance that monitoring and surveillance data reporting has on measuring the success of our actions, one of the key commitments outlined is the strengthening of Canada's national surveillance systems<sup>4</sup>.

This report provides an update on the epidemiology of three nationally notifiable STIs in Canada: chlamydia, gonorrhea and infectious syphilis (including congenital syphilis) using data up to 2018, by province/territory, age group and sex. In addition, updated information related to syphilis collected through the Public Health Agency of Canada (PHAC) Syphilis Outbreak Investigation Coordination Committee (SOICC) have been included.

## 3.0 Methods

### 3.1 Data Sources

In Canada, the surveillance of nationally notifiable diseases is conducted by the PHAC in coordination with provincial and territorial governments via the Canadian Notifiable Disease Surveillance System (CNDSS)<sup>5</sup>. Provincial and territorial health authorities provide non-nominal data on laboratory-confirmed cases. Variables submitted by all reporting jurisdictions are: age at diagnosis, year of diagnosis, province/territory of diagnosis, and sex. As such, national reporting is limited to analyses of these variables. CNDSS staff validate the reported data with the submitting province or territory during data processing to resolve data errors or inconsistencies and maximize accuracy. Chlamydia has been nationally notifiable since 1991 while gonorrhea and syphilis have been notifiable since 1924<sup>6</sup>. Extracts from the CNDSS are used as the basis for national surveillance reports; this report is based on data extracted in April 2020. Historical data for all three nationally notifiable STIs (chlamydia, gonorrhea and infectious syphilis) were available from all provinces and territories from 2009 to 2017. For 2018, data from British Columbia was not available, and as such, not included in the analyses for 2018.

In July 2019, PHAC established a SOICC to support the coordination of the Canadian response in dealing with the rise in the number of syphilis cases and jurisdictionally declared outbreaks. All of the provinces and territories have collected and shared with PHAC preliminary 2018 enhanced syphilis surveillance data.

### 3.2 Case Definitions

Case definitions for all three nationally notifiable STIs are available [online](#).

### 3.3 Data Analysis

A descriptive analysis of reported chlamydia, gonorrhea and infectious syphilis cases by year, age group and sex was conducted using data reported to the CNDSS using SAS, SPSS and Microsoft Excel. All reported cases of chlamydia and gonorrhea are included in national-level analysis. Only data on infectious syphilis cases (including primary, secondary, early latent and infectious neurosyphilis stages) are presented in this report.

National annual rates of reported cases of chlamydia, gonorrhea and infectious syphilis were computed using the number of cases from the CNDSS as numerators and Statistics Canada 2018 yearly population estimates as denominators. Rates, percentages and change in rates were calculated using unrounded numbers; no statistical procedures were used for comparative analyses. Observed trends over time must be interpreted with caution, as rates based on small numbers are prone to fluctuation over time. Previous reports may present different rates for some years due to improved diagnostic capabilities, improved duplicate removal, shortened reporting delay and changes in reporting practices at the jurisdictional level.

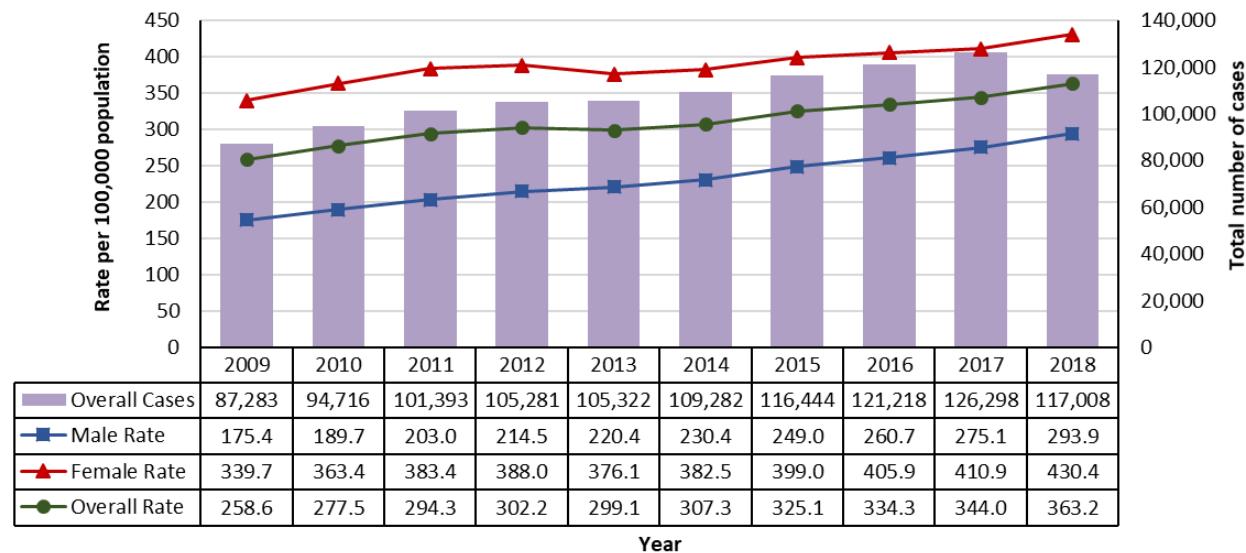
Supplementary tables are listed in Appendix A and are available upon request.

## 4.0 Chlamydia

Chlamydia, an infection caused by *Chlamydia trachomatis*, has been nationally notifiable since 1991 and remains the most commonly reported bacterial STI in Canada<sup>7</sup> and worldwide with an estimated 127 million cases globally in 2018<sup>8</sup>. Rates have been increasing steadily since 1997<sup>2</sup>. Since asymptomatic infections are common in men and women, affected individuals unaware of their status<sup>9</sup>, in the absence of screening, can contribute to the spread of infection.

The number of rates of reported chlamydia cases continue to increase. In Canada, between 2009 and 2018, the number of reported chlamydia cases increased steadily, from 87,283 to 117,008. The corresponding overall rate in 2018 was 363.2 cases per 100,000 population, an increase of 40.5% from 2009 (Figure 1). On average, over the past decade, nationally reported chlamydia rates have increased by 5.0% per year.

**Figure 1. Overall<sup>a</sup> and sex-specific rates of reported chlamydia cases in Canada, 2009-2018\***



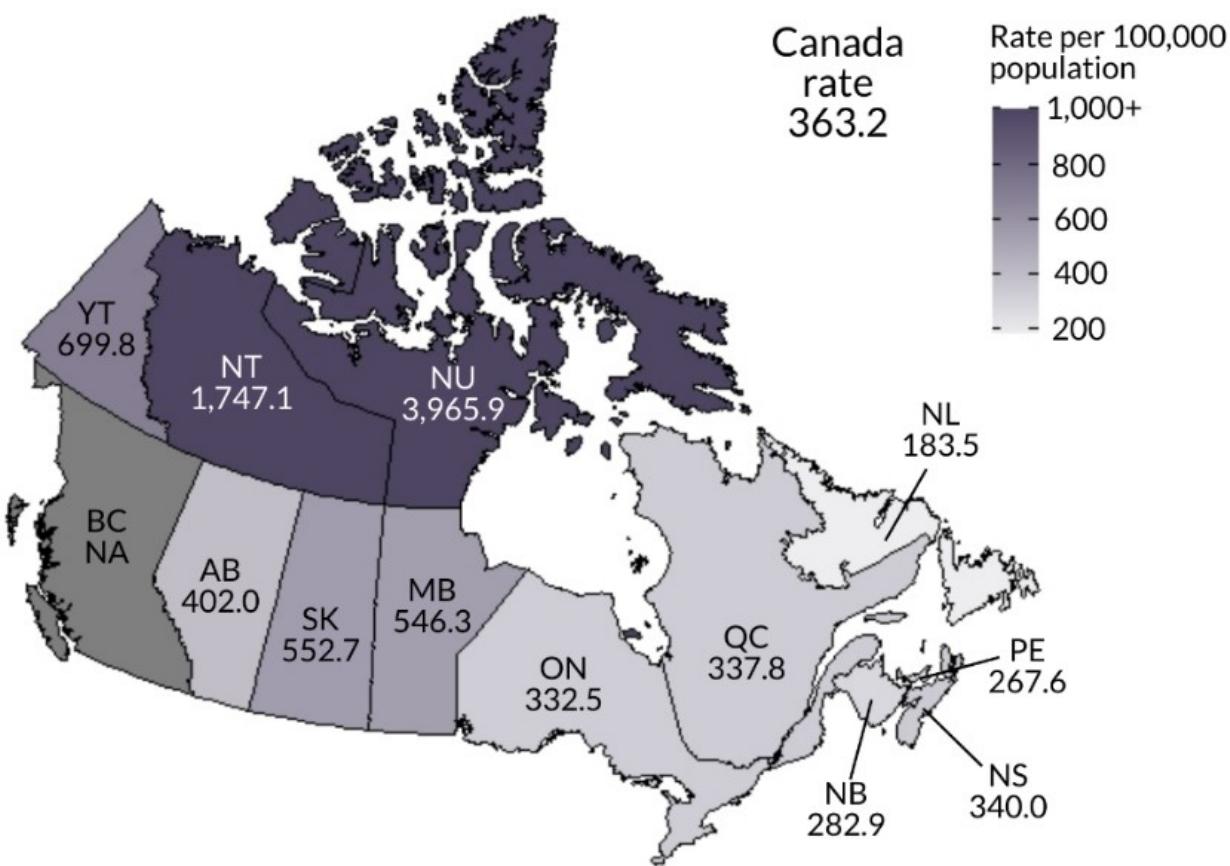
<sup>a</sup>Overall includes unspecified sex.

\*2018 data does not include British Columbia.

### 4.1 Geographic Distribution

Rates of reported chlamydia cases varied by province and territory. In 2018, rates ranged from 183.5 in Newfoundland and Labrador to 3,965.9 cases per 100,000 population in Nunavut. The highest rates were among people from the Northern territories, with rates of 699.8 per 100,000 (Yukon), 1,747.1 cases per 100,000 (Northwest Territories) and 3,965.9 (Nunavut). The three territories have held the highest rates across Canada over the past decade. In addition, Alberta, Manitoba and Saskatchewan reported rates above the Canadian rate of 363.2 (402.0, 546.3 and 552.7 cases per 100,000 population respectively) (Figure 2).

Figure 2. Rates of reported chlamydia cases in Canada, by province/territory, 2018



NA: Not available.

Although the highest rates were observed in the three territories, the largest relative increases in rates since 2009 were occurring elsewhere in Canada. Prince Edward Island had the largest relative rate increase in the past decade (86.3%), from 143.7 to 267.6 cases per 100,000 population, and Newfoundland had the second largest increase (78.0%) from 103.1 to 183.5 cases per 100,000 population. Notably, the only province/territory to experience a decrease in rate was the Northwest Territories, decreasing 26.3% from 2,369.3 cases per 100,000 in 2009 to 1,747.1 cases per 100,000 in 2018.

## 4.2 Age and Sex Distribution

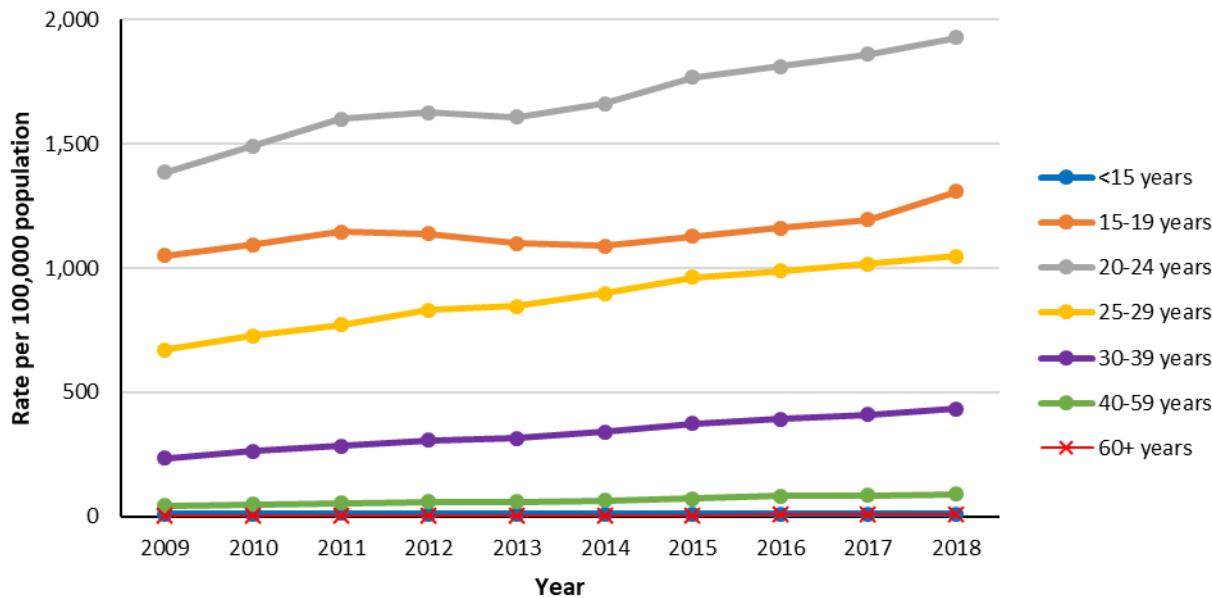
In 2018, more than three quarters (76.1%) of reported chlamydia cases were among people less than 30 years of age. This is similar to what is seen in gonorrhea, but in contrast to infectious syphilis, in which the same age groups accounted for only 37.8%. People between the ages of 15 to 24 accounted for more than half (55.6%) of the reported chlamydia cases in 2018.

Overwhelmingly, females accounted for the majority of cases in the younger age groups. Females less than 30 years of age accounted for 48.9% of all cases in 2018, whereas males of the same age group accounted for 27.1% of all cases. Nearly one-quarter (22.0%) of all cases

occurred in females between the ages of 20 and 24 years. Among cases 30 years of age and older, males accounted for the majority of cases.

The highest rates of reported chlamydia cases were among the 20 to 24 year age group (1,928.8 cases per 100,000 population), followed by the 15 to 19 and 25 to 29 year age groups (1,308.9 and 1,047.9 cases per 100,000, respectively) (Figure 3).

**Figure 3. Rates of reported chlamydia cases in Canada, by age group and year, 2009-2018\***

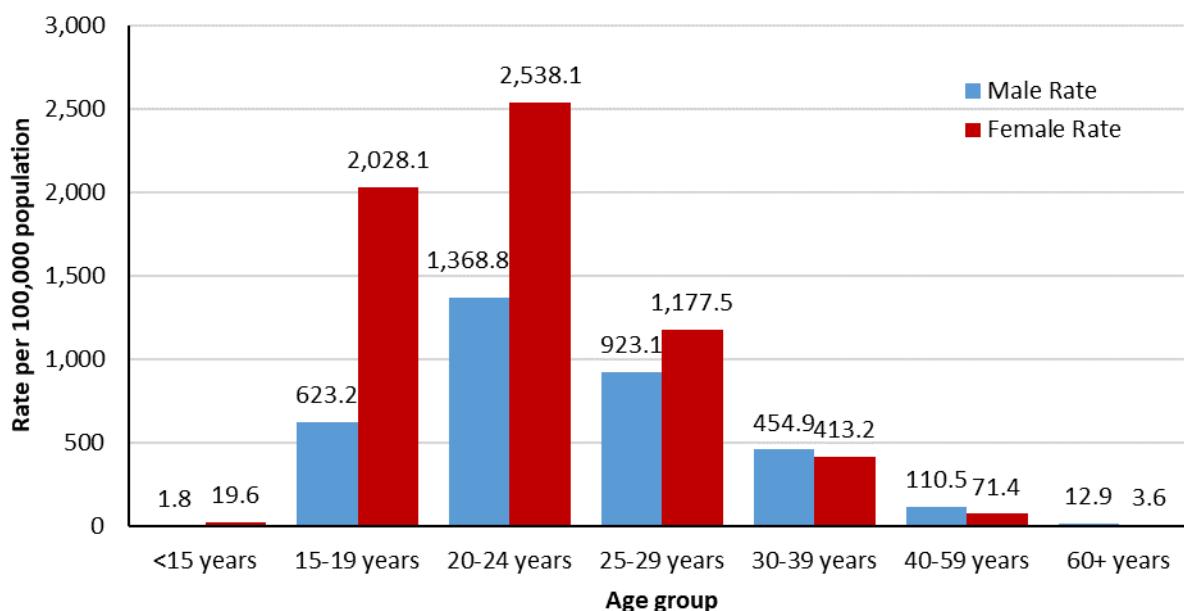


\*2018 data does not include British Columbia.

Since 2009, all age groups experienced an increase in rate except for those under 15 years of age, although the magnitude of this change varied by age group. People in the 20 to 24 year age group had the largest absolute rate difference, increasing by 543.5 cases per 100,000 population (39.2% increase) since 2009.

Older cohorts (those 30 years of age and over) had the lowest rates but experienced the largest relative change in rate in the past ten years. The relative change in rate increased with advancing age. Between 2009 and 2018, people 60 years of age and older had the largest relative increase in rate (133.5%), from 3.4 to 8.0 cases per 100,000 population, followed by those in the 40 to 59 age group (109.0%), going from 43.6 to 91.1 cases per 100,000 population.

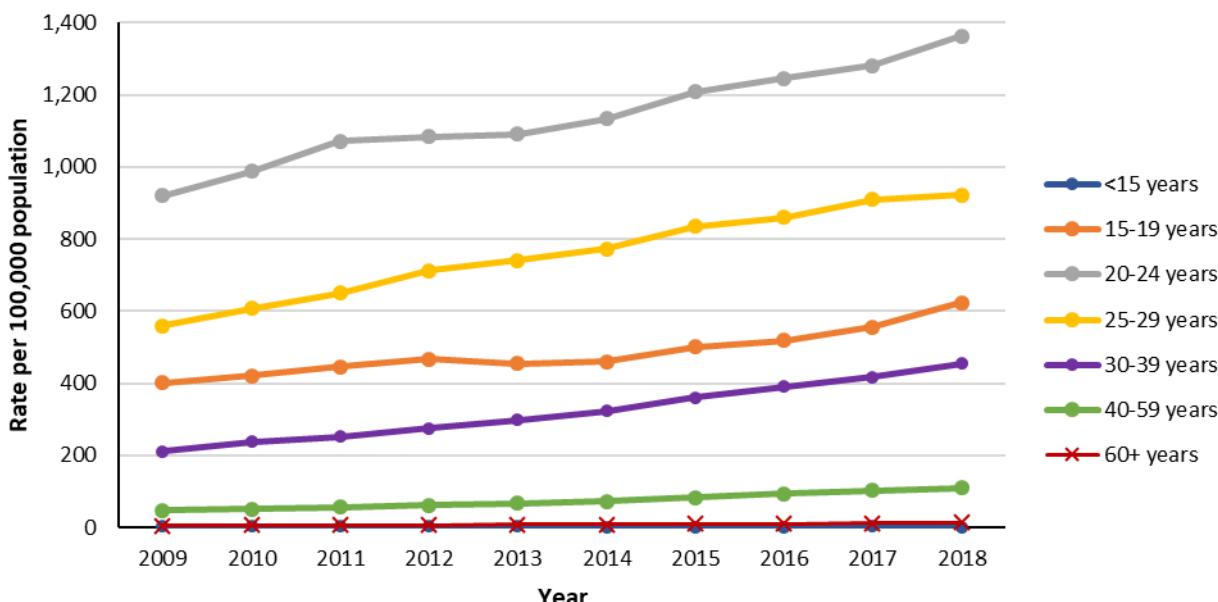
In both women and men, the highest reported rates of chlamydia infections were in 20 to 24 year olds, although the rate in women (2,538.1 per 100,000 females) was almost twice as high as that in men (1,363.8 per 100,000 males). The ratio of female to male rates decreased with age. In the 30 years and older age groups, rates were higher in men than in women (Figure 4).

**Figure 4. Rates of reported chlamydia cases in Canada, by sex and age group, 2018\***

\*2018 data does not include British Columbia.

For every year between 2009 and 2018, female rates were higher than male rates among the younger populations (less than 40 years of age), except for 2017 onward when male rates began to be slightly higher than female rates among the 30-39 age group. Accordingly, male rates were consistently higher than female rates among people over 40 years of age.

Over the past decade, among both males and females, the highest rate of reported chlamydia infections was seen in those under 30. Conversely, the greatest relative increase were seen in the age groups over 40 (Figure 5 and Figure 6).

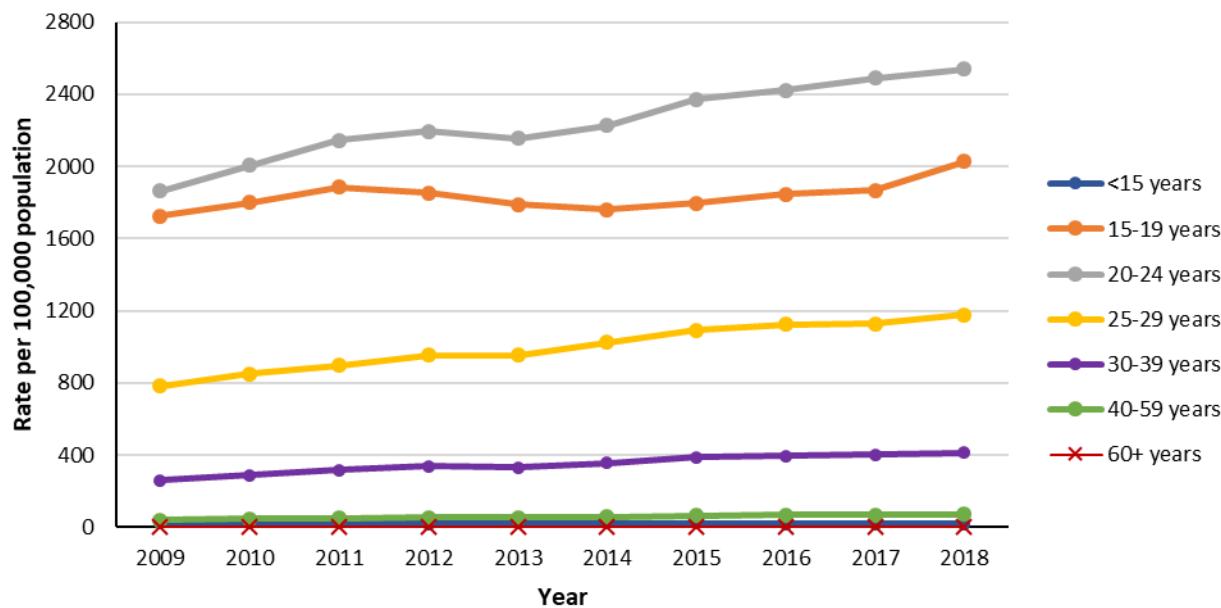
**Figure 5. Male rates of reported chlamydia cases in Canada, by age group and year, 2009-2018\***

\*2018 data does not include British Columbia.

Although reported rates in older men remained low compared to other age groups, substantial increases were seen since 2009. Between 2009 and 2018, reported rates in 40 to 59 years olds increased by 135.3% (from 47.0 to 110.5 per 100,000 males) and by 163.2% in those 60 years of age and older (from 4.9 to 12.9 per 100,000 males) (Figure 5).

Among women, the highest rates are consistently seen among the younger age groups: 20-24, followed by 15-19 and 25-29 year olds. While reported rates in older women remained low compared to other age groups, substantial increases were seen since 2009. Between 2009 and 2018, reported rates in 40 to 59 year olds increased by 78.4% (from 40.0 to 71.4 per 100,000 females) and by 68.4% in those 60 years of age and older (from 2.2 to 3.6 per 100,000 females) (Figure 6).

**Figure 6. Female rates of reported chlamydia cases in Canada, by age group and year, 2009-2018\***



\*2018 data does not include British Columbia.

In all provinces and territories, rates of reported cases of chlamydia were highest among those aged 20 to 24 years in 2018. With the exception of Prince Edward Island, those aged 15 to 19 years had the second highest rates in 2018. For Prince Edward Island, the second highest rates were among those aged 25 to 29 years.

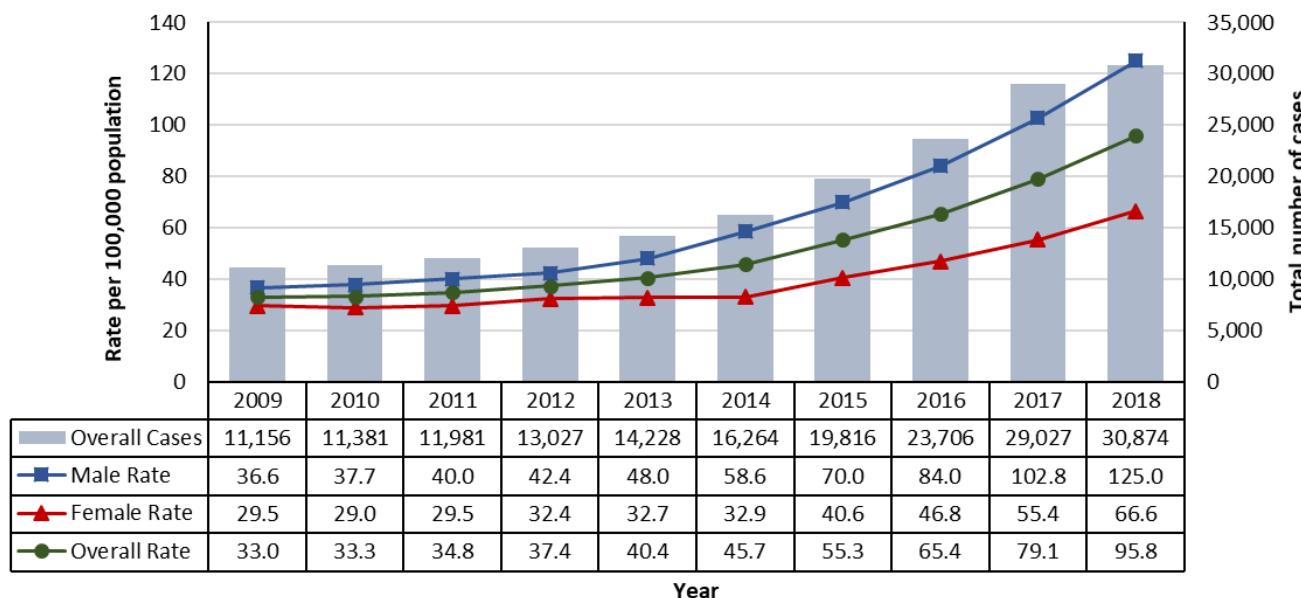
The majority of cases were female in each jurisdiction, and the proportion of cases by sex in provinces and territories remained fairly close to the national proportions of 60% female cases and 40% male.

## 5.0 Gonorrhea

Gonorrhea, an infection caused by *Neisseria gonorrhoeae*, has been nationally notifiable since 1924 and remains the second most commonly reported bacterial STI in Canada<sup>10</sup>. Untreated gonococcal infections can lead to complications for both sexes, with more severe consequences for women<sup>10</sup>.

From 2009 to 2012, the number and rate of reported gonorrhea cases remained relatively stable. Following 2012, the number and rate of reported gonorrhea cases began increasing. In 2018, 30,874 cases of gonorrhea were reported nationally, corresponding to a rate of 95.8 cases per 100,000 population. On average, over the past decade, nationally reported gonorrhea rates have increased by 9.4% per year. The increase of reported cases between 2017 and 2018 was sharper than previous years with an increase of 21.2%, from 79.1 to 95.8 per 100,000 (Figure 7).

**Figure 7. Overall<sup>a</sup> and sex-specific rates of reported gonorrhea cases in Canada, 2009-2018\***



<sup>a</sup>Overall includes unspecified sex.

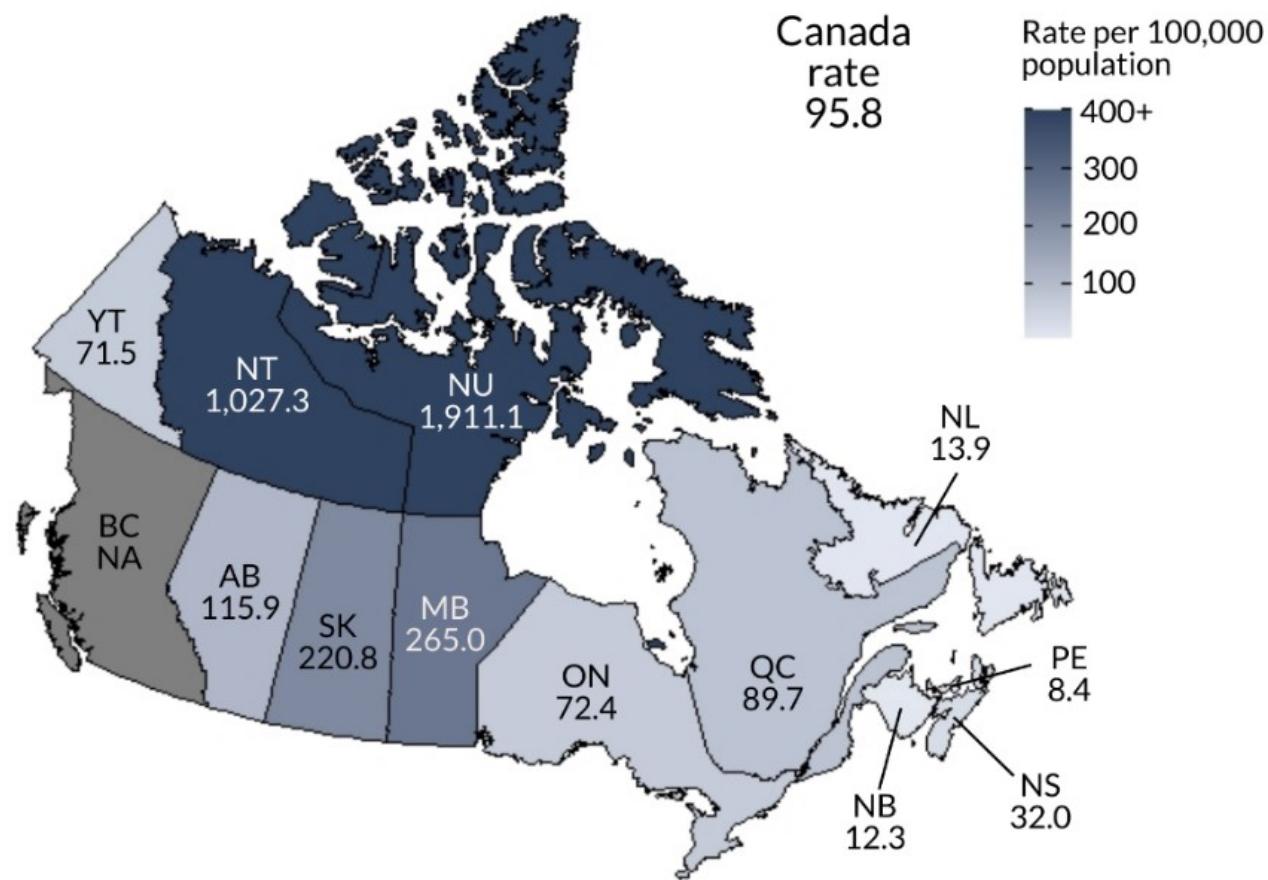
\*2018 data does not include British Columbia.

## 5.1 Geographic Distribution

Rates of reported gonorrhea in 2018 varied by province and territory ranging from 8.4 cases per 100,000 population in Prince Edward Island to 1,911.1 cases per 100,000 population in Nunavut. In 2018, the highest number of gonorrhea cases were reported in the most populated provinces - Ontario (33.8%), Quebec (24.4%), and Alberta (16.2%). However, reported rates were highest in two Territories (Figure 8).

Since 2009, the highest rates have been among Nunavut and the Northwest Territories, both with rates above 1,000 cases per 100,000 population in 2018. Manitoba had the third highest rate in 2018 with 265.0 cases per 100,000 population. The Atlantic provinces (New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland) have held the lowest rates of reported gonorrhea cases since 2009.

Figure 8. Rates of reported gonorrhea cases in Canada, by province/territory, 2018



NA: Not available.

Since 2009, the rate of reported cases of gonorrhea increased in all provinces and territories. Between 2009 and 2018, the greatest increase in reported gonorrhea rates occurred in Prince Edward Island, with an increase of 1,078.7% and Newfoundland, with an increase of 621.3%. Despite these large increases, the overall number of cases remain small (13 cases in Prince Edward Island and 73 cases in Newfoundland).

## 5.2 Age and Sex Distribution

Since 2009, males comprised the majority of reported gonorrhea cases in Canada, ranging from 54.8% in 2009 to 64.8% in 2018. In 2018, the national male-to-female gonorrhea ratio was 1.9:1.0, reflecting that more men than women were diagnosed with gonorrhea. Between 2009 and 2018, rates in males increased by 241.9% from 36.6 to 125.0 per 100,000 males and rates in females increased by 125.5%, from 29.5 to 66.6 per 100,000 females. The 2018 reported rate among men was nearly twice as high as the female rate, with 125.0 cases per 100,000 males compared to 66.6 cases per 100,000 females. Male rates are also increasing more quickly than female rates, creating a wider gap between male and female rates (Figure 7).

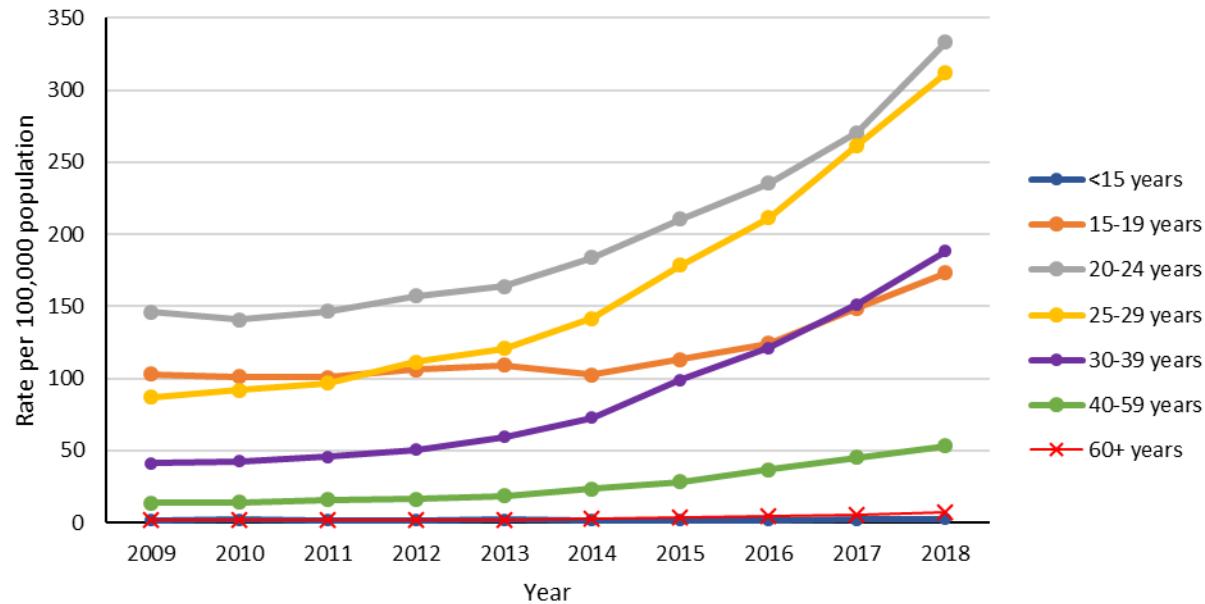
Reported rates of gonococcal infections in 2018 were highest in the 20 to 24 year (333.1 per 100,000 population) and 25 to 29 year (311.9 per 100,000 population) age groups. Since 2009, all age groups experienced an increase in rate. From 2009 to 2011, 15 to 19 year olds

experienced the second highest reported rates of gonorrhea. Starting in 2012, the second highest reported rates of gonorrhea were among the 25 to 29 year olds. In 2017 and 2018, the 30 to 39 year age group overtook the 15 to 19 year age group with the third highest rates (Figure 9).

Nearly three-quarters (72.4%) of the reported gonorrhea cases were among 20 to 39 years olds in 2018. This is similar to what is seen in chlamydia (71.5%), but in contrast to infectious syphilis, in which the same age groups accounted for only 62.5%. People under 30 years of age accounted for more than half (56.3%) of the reported gonorrhea cases in 2018.

In 2018, males 20 years of age and older accounted for 60.9% of all cases, whereas females from these same age groups accounted for 28.1% of all cases. More than one-quarter (27.8%) of cases occurred in males between 20 and 29 years of age. Out of all cases, those that were 40 years of age and older, males accounted for 13.8% and females accounted for 2.9%.

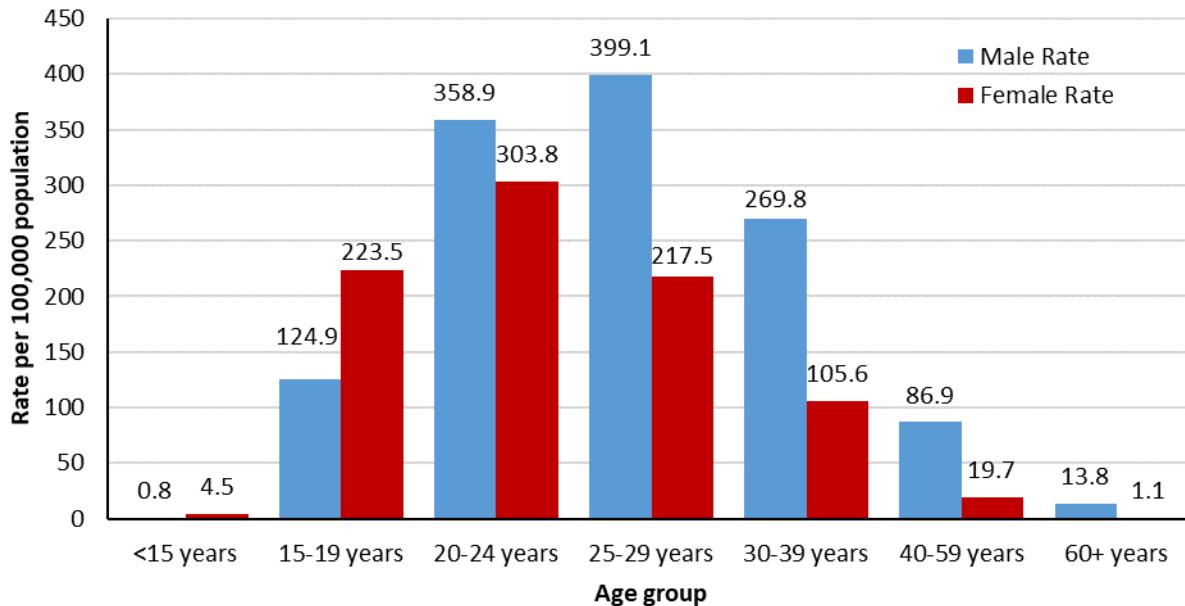
**Figure 9. Rates of reported gonorrhea cases in Canada, by age group and year, 2009-2018\***



\*2018 data does not include British Columbia.

The magnitude of the change in rate over time varied by age group. The 25 to 29 year age group increased the most, up 225.0 cases per 100,000 population since 2009. Notably, compared to 2009, all age groups above 19 years of age more than doubled in rate, with those over the age of 25 more than tripling the rate.

In all provinces and territories, rates of reported cases of gonorrhea were highest among those aged 20 to 24 in 2018, except for Prince Edward Island and Yukon, where rates were higher in those 25 to 29.

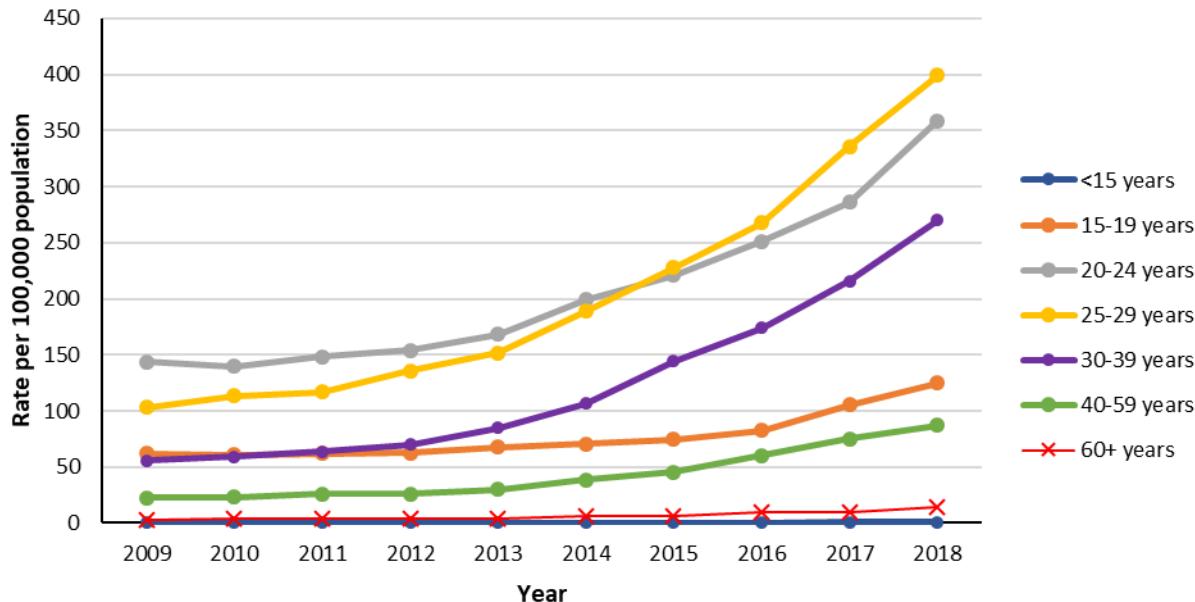
**Figure 10. Rates of reported gonorrhea cases in Canada, by sex and age group, 2018\***

\*2018 data does not include British Columbia.

In 2018, the highest reported rate of gonorrhea infections in males was in the 25 to 29 year age group (399.1 per 100,000 males), followed by the 20 to 24 year old (358.9 per 100,000 males) age group. Among females, the highest reported rate was in 20 to 24 year age group (303.8 per 100,000 females), followed by 15 to 19 year olds (223.5 per 100,000 females) (Figure 10).

Between 2009 and 2018, male rates were consistently higher than female rates among people older than 20 years of age (Figure 11 and Figure 12). In 2018, male rates for those above 29 years of age were more than double those among their female counterparts. From 2009 to 2014, males between the ages of 20 and 24 years experienced the highest rates of gonorrhea. There was a shift in 2015, with the highest rates among males occurring in those between the ages of 25 to 29 years (Figure 11).

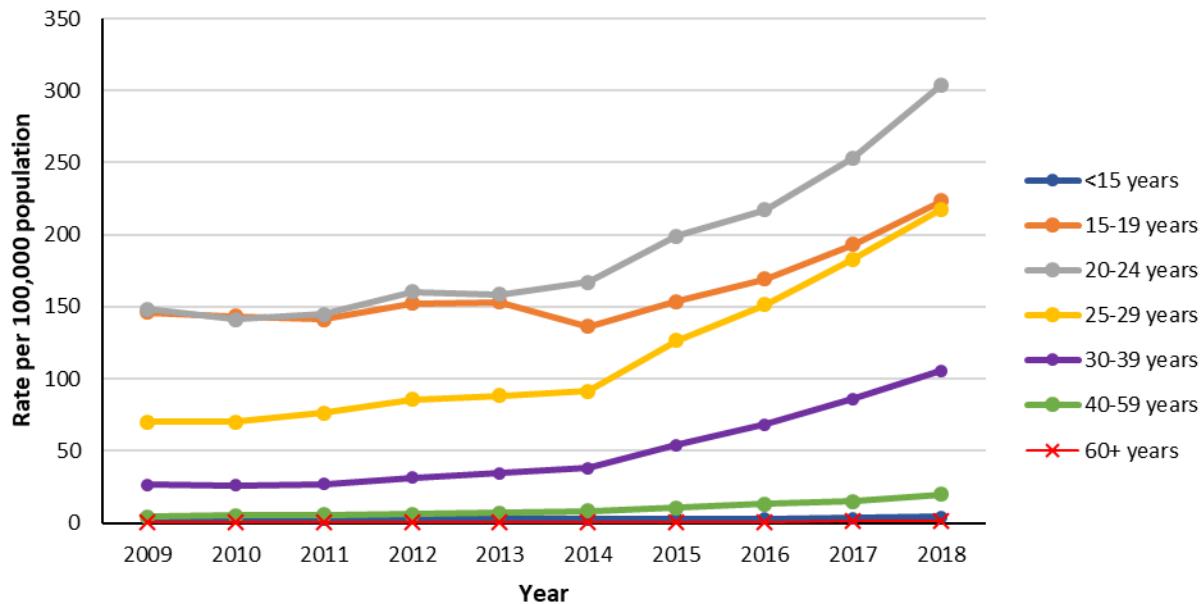
Over the past decade, rates increased in all age groups among males, with the greatest absolute increase in rates of reported gonococcal infections observed in 25 to 29 year olds. The rate increased from 103.4 per 100,000 males in 2009 to 399.1 per 100,000 males, an increase of 295.6 per 100,000 males, or 285.8%. Although reported rates in both youth and older men remained low compared to other age groups, substantial increases were seen since 2009. Between 2009 and 2018, reported rates in males 60 years and older increased by 337.7% (from 3.1 to 13.8 per 100,000 males) and by 302.5% in those less than 15 years old (from 0.4 to 1.7 per 100,000 males) (Figure 11).

**Figure 11. Male rates of reported gonorrhea cases in Canada, by age group and year, 2009-2018\***

\*2018 data does not include British Columbia.

Between 2009 and 2018, female rates were consistently higher than male rates in the younger age groups (less than 20 years of age). In 2018, female rates for those 15 to 19 years of age were almost 50% greater among their male counterparts (Figure 11 and Figure 12).

In females, between 2009 and 2018, the greatest absolute increase in reported rates of gonorrhea was seen in 20 to 24 year olds. The rate increased by 155.4, from 148.4 to 303.8 cases per 100,000 females, or 104.7%. The greatest relative increase was seen in 40 to 59 year olds, which increased by 348.5%, from 4.4 to 19.7 cases per 100,000 females. Despite lower reported rates than those reported in males, between 2009 and 2018, reported rates in females 30 to 39 year of age increased by 297.4% (from 26.6 to 105.6 cases per 100,000 females), by 348.5% in 40 to 59 year olds (from 4.4 to 19.7 cases per 100,000 females), and by 155.1% in those 60 years and older (from 0.4 to 1.1 cases per 100,000 females) (Figure 12).

**Figure 12. Female rates of reported gonorrhea cases in Canada, by age group and year, 2009-2018\***

\*2018 data does not include British Columbia.

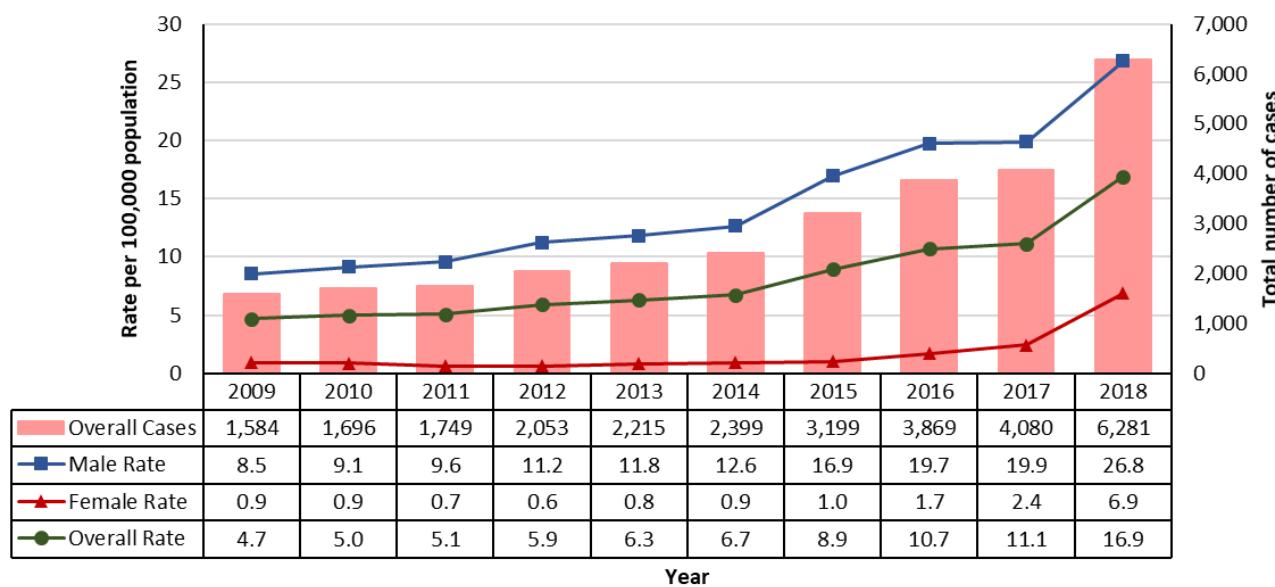
The proportion of male cases ranged from 41.3% to 77.8% across provinces and territories in 2018. Ten provinces and territories reported having a greater proportion of male cases - the provinces with the greatest proportion of male cases were Ontario (72.6%) and Quebec (77.8%). Manitoba (53.9%), Saskatchewan (54.4%) and Nunavut (58.7%) reported having a greater proportion of female cases.

## 6.0 Infectious Syphilis

Syphilis, an infection cause by the bacterium *Treponema pallidum*, has been nationally notifiable since 1924<sup>11</sup>. Left untreated, it progresses through different stages, with primary, secondary and early latent (less than one year after the point of infection) stages being infectious<sup>11</sup>. Only these infectious stages are included in this report.

The number and rate of reported infectious syphilis cases are increasing. In 2018, 6,281 cases of infectious syphilis were reported nationally, corresponding to a national rate of 16.9 cases per 100,000 population. Since 2009, the number of infectious syphilis cases has more than tripled (1,584 cases and a rate of 4.7 per 100,000 population in 2009). Infectious syphilis had the highest increase in rates of all STIs with more than 259.5% increase over the past decade. On average, over the past decade, nationally reported infectious syphilis rates have increased by 12.8% per year. (Figure 13).

**Figure 13. Overall<sup>a</sup> and sex-specific rates of reported infectious syphilis cases in Canada, 2009-2018**

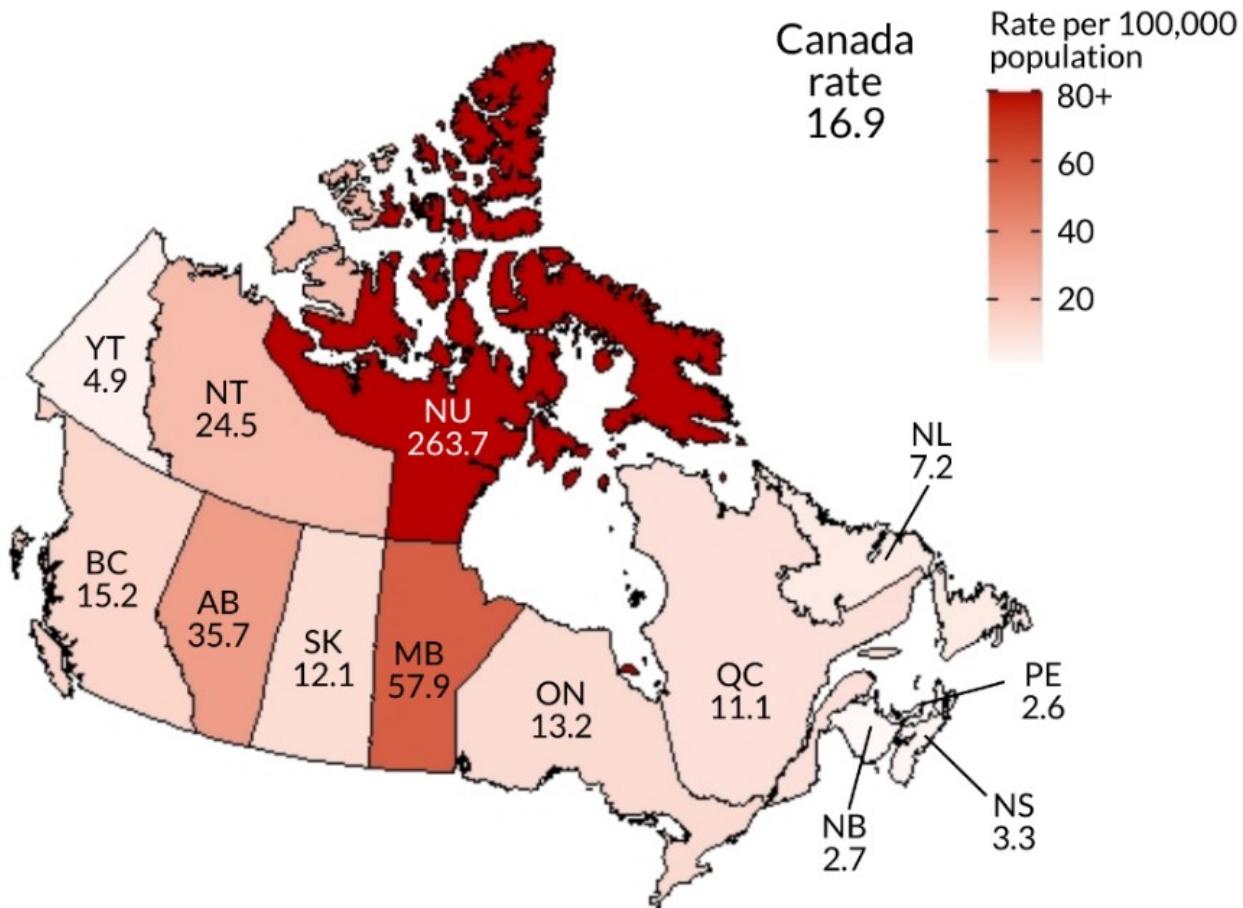


<sup>a</sup>Overall includes unspecified sex.

### 6.1 Geographic Distribution

Rates of reported infectious syphilis in 2018 varied by province and territory, ranging from 2.6 in Prince Edward Island to 263.7 per 100,000 population in Nunavut. Nunavut reported the highest rate in Canada every year since 2012, ranging from 83.2 cases per 100,000 population in 2012 to 263.7 cases per 100,000 population in 2018. For the past five years, Manitoba held the next highest rates, from 9.2 cases per 100,000 population in 2014 and increasing to 57.9 cases per 100,000 population in 2018. The Atlantic provinces of New Brunswick, Nova Scotia and Prince Edward Island had the lowest rates in Canada in 2017 and 2018 (Figure 14).

Figure 14. Rates of reported infectious syphilis cases in Canada, by province/territory, 2018



Nunavut reported one of the lowest relative increase in rate since 2014 (up 16.1%, from 227.1 per 100,000 population in 2014 to 263.7 per 100,000 population in 2018). Between 2009 and 2018, the greatest increase in reported infectious syphilis rates occurred in Manitoba, with an increase of 13,943.8%, from 0.4 per 100,000 population in 2009 to 57.9 per 100,000 population in 2018. Conversely, the Northwest Territories experienced a 68.1% decrease. Since 2014, only three provinces (New Brunswick, Nova Scotia and Prince Edward Island) experienced a decrease in rates, while all others experienced an increase in rates. Yukon and Northwest Territories reported between 0 and 5 cases annually in the past five years (2014-2018).

## 6.2 Age and Sex Distribution

Over the past decade, males comprised the large majority (greater than 85%) of reported infectious syphilis cases every year. In 2018, the male rate was more than three times higher than the female rate, with 26.8 cases per 100,000 males compared to the female rate of 6.9 cases per 100,000 females (Figure 13). The rate increase in females was quite steep from 2017 to 2018 with a relative rate increase of 184.7% (from 2.4 to 6.9 cases per 100,000 population). Although male rates were higher, the relative increase in rate was higher among females in the past decade (648.3% versus 214.6%).

The male-to-female rate ratio decreased from 9.2:1.0 in 2009 to 3.9:1.0 in 2018, reflecting that more males than females were reported with infectious syphilis, but that this trend decreased over time. Nationally, 78.9% of reported syphilis cases were male and 20.6% of cases female in

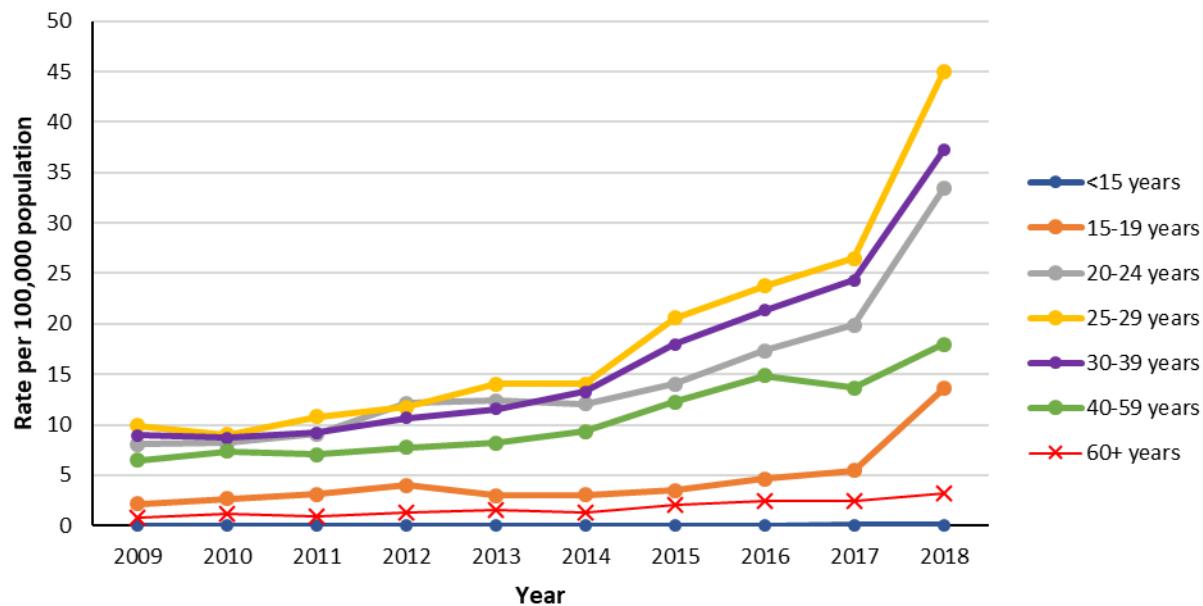
2018. The majority of provinces and territories reported a greater proportion of cases being male. New Brunswick reported the greatest proportion of male cases (95%) while Yukon and Nunavut reported the lowest proportion of male cases (50%). Across the country, the male-to-female rate ratio ranged from highest in British Columbia (23.7:1) to lowest in Nunavut (0.9:1).

Compared to 2009, all age groups over 15 years of age increased. The 15 to 19 age group increased more than six-fold from 2009 to 2018, from 2.2 to 13.6 cases per 100,000. Since 2009, only twelve cases were reported among those aged 10 to 14 years old and no cases were reported among those under 10 years of age (Figure 15).

Since 2014, the highest rates of reported infectious syphilis cases were among the 25 to 29 and 30 to 39 year age groups, followed by the 20 to 24 age group. People 15 years of age and younger and those over 60 held the lowest rates in all years since 2009 (at or under 3 cases per 100,000) (Figure 15).

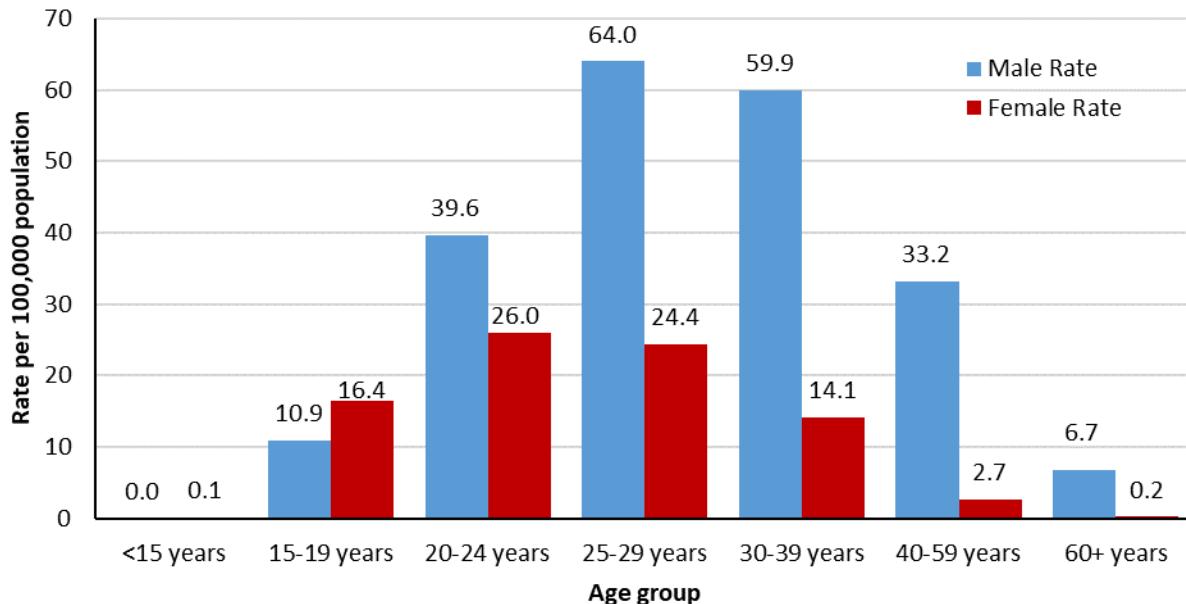
In 2018, nearly half (49.0%) of reported infectious syphilis cases in Canada were among people aged between 25 and 39 years. Almost one-quarter (21.7%) of all cases occurred in males between 20 and 29 years of age. Out of all cases, males 40 years of age and older accounted for 31.0% and females accounted for 2.4%.

**Figure 15. Rates of reported infectious syphilis cases in Canada, by age group and year, 2009-2018**

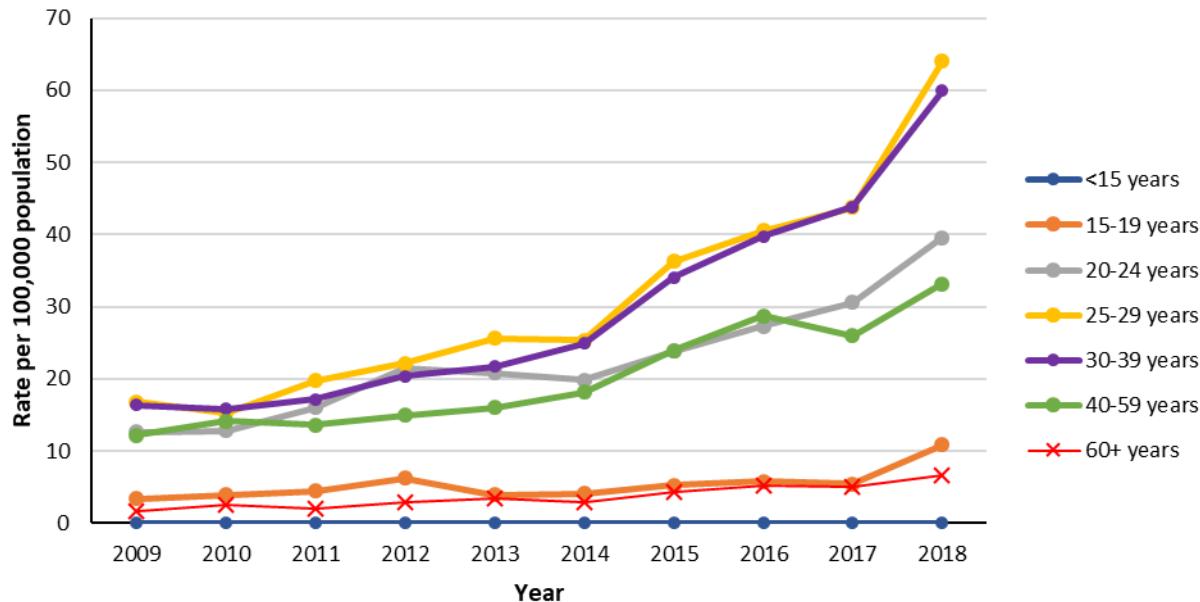


In 2018, the proportion of cases attributed to males increased with increasing age. Males comprised 41.2% of the cases among 15 to 19 year olds and 96.5% of the cases among those 60 years of age and older. In men, the highest reported rates of infectious syphilis was in the 25 to 29 year olds (64.0 per 100,000 males), although in women, the highest reported rate was in the 20 to 24 years olds (26.0 per 100,000 females) (Figure 16).

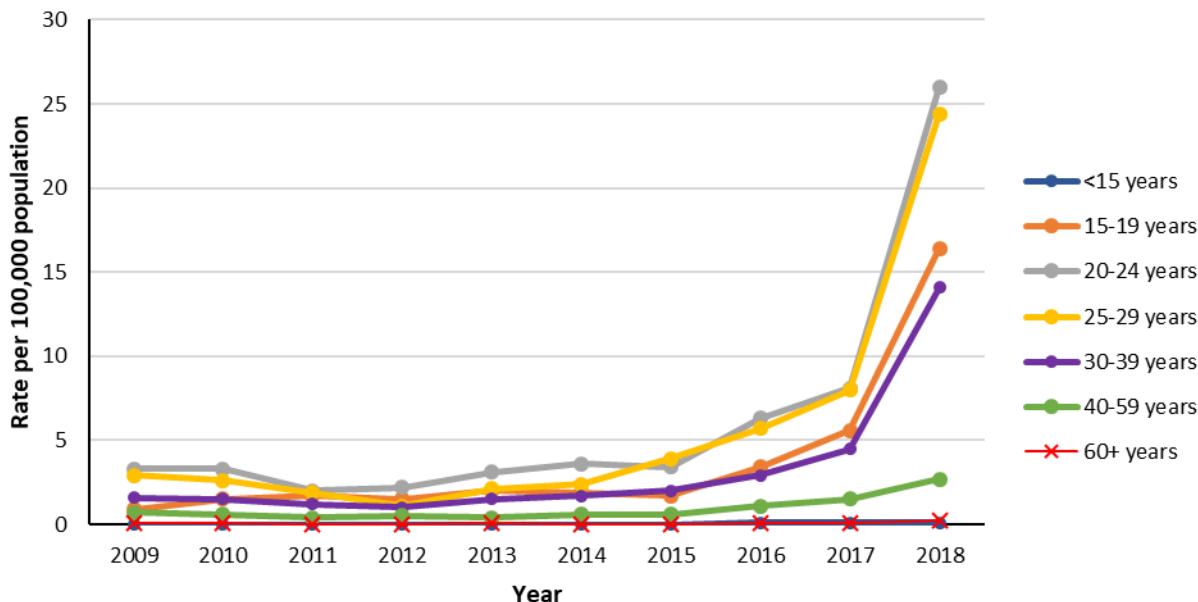
**Figure 16. Rates of reported infectious syphilis cases in Canada, by sex and age group, 2018**



Over the past decade, among males aged 25 to 29 years old, the reported rate increased from 16.9 per 100,000 males in 2009 to 64.0 per 100,000 males in 2018 (Figure 17), an increase of 47.1 cases per 100,000 males, or 279.7% increase. Although reported rates for both youth less than 20 and older men remained low compared to other age groups, substantial increases were seen since 2009. Between 2009 and 2018, reported rates in males 15 to 19 years older increased by 222.7%, from 3.4 to 10.9 per 100,000 males. Rates among males 60 years of age and older increased by 302.2% - the largest relative increase among males in all groups - from 1.7 to 6.7 per 100,000 males (Figure 17).

**Figure 17. Males rates of reported infectious syphilis cases in Canada, by age group and year, 2009-2018**

Although reported rates in females remained low from 2009 to 2018, substantial increases in all age groups 15 years and older were seen. Between 2009 and 2018, the greatest absolute increase in reported rates of infectious syphilis was seen in 20 to 24 year olds, increasing by 22.7 cases per 100,000, from 3.3 per 100,000 in 2009 to 26.0 per 100,000 in 2018 (Figure 18), corresponding to an increase of 693.3%.

**Figure 18. Female rates of reported infectious syphilis cases in Canada, by age group and year, 2009-2018**

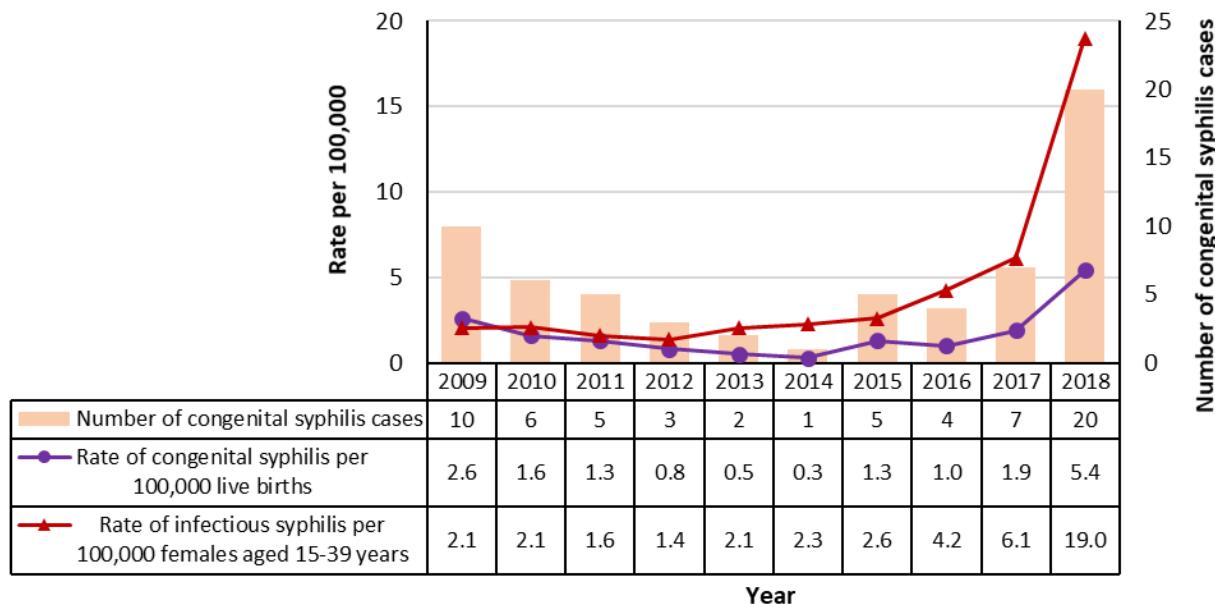
In the majority of provinces and territories, the highest rates of reported cases of infectious syphilis were among those aged 20 to 24 or 25 to 29 in 2018. However, in Nova Scotia and Newfoundland and Labrador, the highest rates were reported in the 30 to 39 year age.

## 6.3 Congenital Syphilis

Congenital syphilis is caused by the vertical transmission of *Treponema pallidum* from a pregnant individual infected with syphilis to their fetus. Congenital syphilis may not be diagnosed until later in life, as the disease can often be asymptomatic for life or may present with symptoms that are not identified in the first few weeks<sup>11,120</sup>. Only early congenital syphilis cases (diagnosed in those under two years of age) are reported nationally<sup>6</sup>.

The number of confirmed congenital syphilis cases reported in Canada varied from one to 20 cases per year from 2009 to 2018 (Figure 19). Between 2009 and 2014, a downward trend was observed in reported cases (high of 10 cases in 2009 and a low of one case reported in 2014) followed by increase of up to twenty reported cases in 2018. From 2017 to 2018, there was a 188.8% increase in rate of congenital syphilis cases (from 1.9 to 5.4 cases per 100,000 live births). Among females aged 15 to 39 years, a 211.5% increase in rate of infectious syphilis was observed between 2017 and 2018 (from 6.1 to 19.0 cases per 100,000 females). Changes in rate should be interpreted with caution due to low case numbers (Figure 19).

**Figure 19. Number of reported cases and rates of congenital syphilis and female rate (age 15-39) of infectious syphilis in Canada, 2009-2018**



## 7.0 Discussion

STIs continue to remain a significant public health challenge in Canada, and the epidemic disproportionately affects certain populations. Over the past decade, rates for all STIs have increased dramatically. In addition, it is possible that many cases of chlamydia, gonorrhea and infectious syphilis continue to go undiagnosed and unreported. Strong public health infrastructure is critical to prevent and control STIs, especially among the most vulnerable groups.

Chlamydia continues to be the most commonly reported STI in Canada with 117,008 cases reported across Canada in 2018 (Note: 2018 numbers for chlamydia and gonorrhea do not include British Columbia).

Over the past decade, increases in the rates of reported cases of chlamydia have been observed in Canada despite numerous public health interventions designed to prevent, diagnose and treat infection. The observed increases in rates may be explained by a variety of factors including a true rise in incidence and the implementation of improved detection methods such as more sensitive nucleic acid amplification testing (NAAT) introduced in the mid-1990s. In fact, the introduction of NAAT coincided with the beginning of the historical rise in rates of reported cases of chlamydia. NAAT allows for the use of either urine specimens or swabs, and urine collection is easier and more acceptable to patients. As a result, the number of people, particularly males, being tested has likely increased as well. More screening and more effective contact tracing practices may also have contributed to the observed rise in the rate of reported cases.

Although the rates of reported cases of gonorrhea in Canada are considerably lower than those for chlamydia, rates for both infections appear to be increasing over time. The increase in gonorrhea rates since the late 1990s may be at least partially explained by the factors thought to also affect chlamydia rates, such as the move to more sensitive testing methods and improved case finding<sup>2</sup>. Additionally, both Canadian and other national treatment guidelines emphasize the importance of screening at other anatomical sites in some populations, which may have impacted the increase in the number of cases detected and reported<sup>10,13,14</sup>.

In contrast to chlamydia, observed overall rates of gonorrhea were higher in males. Higher gonorrhea rates among males may be partially explained by the fact that they are more likely than females to have symptomatic infections<sup>15</sup>; the presence of symptoms likely influences care-seeking behaviors and could contribute to the greater number of cases detected among males. In addition, increases in certain sex practices among gay, bisexual and other men who have sex with men (gbMSM) have been associated with increases in gonorrhea in this population<sup>10</sup>. Other high-income countries, including the United States of America, Australia and England have reported similar trends<sup>13,16,17</sup>.

Together with improved testing and screening methods, antimicrobial resistance to the first-line antibiotics also play a role in the rising rates of gonorrhea. Over time, an increasing proportion of *Neisseria gonorrhoeae* isolates has shown resistance to many antibiotics used to treat infection<sup>18,19,20</sup>. In 2018, seven extensively drug resistant gonorrhea isolates were identified in Canada, posing a potential threat to successful treatment<sup>21</sup>. Enhancing surveillance to include linked epidemiological and laboratory data would address the limitation regarding trend interpretation in the current passive surveillance system. The Enhanced Surveillance of

Antimicrobial Resistant Gonorrhea (ESAG) program was initiated by PHAC in 2014 to address this gap<sup>19</sup>.

Although the rates of reported infectious syphilis cases are considerably lower than those for chlamydia and gonorrhea, infectious syphilis had the highest increase in rates of all three STIs from 2009 to 2018 (259.5%) and the number of reported cases almost quadrupled in 2018 compared to 2009. Similar to gonorrhea, and in contrast with chlamydia, observed overall rates of infectious syphilis continue to be higher in males. Although rates of infectious syphilis among females are lower than the male rate, rates are increasing faster among females in recent years; infection in women of childbearing age is of concern because of the potential for congenital syphilis in infants exposed to *Treponema pallidum* prenatally or during childbirth. Screening for syphilis as part of comprehensive prenatal care for all pregnant women, as well as fostering an enabling environment for pregnant individuals to access STBBI care<sup>3</sup>, are both key to preventing congenital syphilis.

Over the past decade, when compared to counties such as the United States<sup>13</sup>, England<sup>16</sup>, and Australia<sup>17</sup>, Canada continues to have the lowest rates of chlamydia, gonorrhea and infectious syphilis. The pattern of higher rates of chlamydia amongst females seen in Canada is similarly seen across these countries. Canada's gonorrhea rates among males are consistently lower than those in these countries, and among females, Canada has the second-lowest rates. Rates of infectious syphilis are increasing in Canada, in the United States<sup>13</sup>, England<sup>16</sup>, and Australia<sup>17</sup>. From 2009 to 2018, Canada reported the lowest rates of infectious syphilis compared to these other countries, although there is some variability in reporting. All of these countries show infectious syphilis rates being significantly higher among males compared to females. The observed difference in rates observed among these countries can likely be attributed, in part, to differences in reporting requirements, screening practices, educational programs, and public health interventions.

Lastly, the surveillance data described in this report have data limitations. Low case counts are sometimes reported for particular infections and certain age groups, such as for congenital syphilis. Therefore, variations in rates over time should be interpreted with caution. Also, data presented in this report likely underestimate the incidence rate of STIs from 2009 to 2018 in Canada, as some infections may be asymptomatic, unscreened, undiagnosed or unreported. Screening, laboratory testing and reporting practices varied across provinces and territories. This means that direct comparison between jurisdictions should be made with caution. Finally, information on risk factors is unavailable in the CNDSS, limiting our ability to identify factors associated with higher STI rates.

STIs continue to remain a serious public health concern in Canada. Over the past decade, reported rates for chlamydia, gonorrhea and infectious syphilis continued to increase substantially.

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## APPENDIX A

These tables and figures are available upon request at: [phac.sti-hep-its.aspc@canada.ca](mailto:phac.sti-hep-its.aspc@canada.ca)

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# Genital Herpes – CDC Fact Sheet



You can get genital herpes even if your partner has no symptoms



**Herpes is a common sexually transmitted disease (STD) that any sexually active person can get. Most people with the virus don't have symptoms. It is important to know that even without signs of the disease, it can still spread to sexual partners.**



## What is genital herpes?

Genital herpes is an STD caused by two types of viruses. The viruses are called herpes simplex type 1 and herpes simplex type 2.

## How common is genital herpes?

Genital herpes is common in the United States. In the United States, about one out of every six people aged 14 to 49 years have genital herpes.

## How is genital herpes spread?

You can get herpes by having oral, vaginal, or anal sex with someone who has the disease.

Fluids found in a herpes sore carry the virus, and contact with those fluids can cause infection. You can also get herpes from an infected sex partner who does not have a visible sore or who may not know he or she is infected because the virus can be released through your skin and spread the infection to your sex partner(s).

## How can I reduce my risk of getting herpes?

The only way to avoid STDs is to not have vaginal, anal, or oral sex.

If you are sexually active, you can do the following things to lower your chances of getting herpes:

- Being in a long-term mutually monogamous relationship with a partner who has been tested and has negative STD test results;
- Using latex condoms the right way every time you have sex.

Herpes symptoms can occur in both male and female genital areas that are covered by a latex condom. However, outbreaks can also occur in areas that are not covered by a condom so condoms may not fully protect you from getting herpes.

## I'm pregnant. How could genital herpes affect my baby?

If you are pregnant and have genital herpes, it is even more important for you to go to prenatal care visits. You need to tell your doctor if you have ever had symptoms of, been exposed to, or been diagnosed with genital herpes. Sometimes genital herpes infection can lead to miscarriage. It can also make it more likely for you to deliver your baby too early. Herpes infection can be passed from you to your unborn child and cause a potentially deadly infection (neonatal herpes). It is important that you avoid getting herpes during pregnancy.

If you are pregnant and have genital herpes, you may be offered herpes medicine towards the end of your pregnancy to reduce the risk of having any symptoms and passing the disease to your baby. At the time of delivery your doctor should carefully examine you for symptoms. If you have herpes symptoms at delivery, a 'C-section' is usually performed.

## How do I know if I have genital herpes?

Most people who have herpes have no, or very mild symptoms. You may not notice mild symptoms or you may mistake them for another skin

condition, such as a pimple or ingrown hair. Because of this, most people who have herpes do not know it.

Genital herpes sores usually appear as one or more blisters on or around the genitals, rectum or mouth. The blisters break and leave painful sores that may take weeks to heal. These symptoms are sometimes called "having an outbreak." The first time someone has an outbreak they may also have flu-like symptoms such as fever, body aches, or swollen glands.

Repeat outbreaks of genital herpes are common, especially during the first year after infection. Repeat outbreaks are usually shorter and less severe than the first outbreak. Although the infection can stay in the body for the rest of your life, the number of outbreaks tends to decrease over a period of years.

You should be examined by your doctor if you notice any of these symptoms or if your partner has an STD or symptoms of an STD, such as an unusual sore, a smelly discharge, burning when urinating, or, for women specifically, bleeding between periods.

### **How will my doctor know if I have herpes?**

Often times, your healthcare provider can diagnose genital herpes by simply looking at your symptoms. Providers can also take a sample from the sore(s) and test it. Have an honest and open talk with your health care provider and ask whether you should be tested for herpes or other STDs.

### **Can herpes be cured?**

There is no cure for herpes. However, there are medicines that can prevent or shorten outbreaks. One of these herpes medicines can be taken daily, and makes it less likely that you will pass the infection on to your sex partner(s).

### **What happens if I don't get treated?**

Genital herpes can cause painful genital sores and can be severe in people with suppressed immune systems. If you touch your sores or the fluids from the sores, you may transfer herpes to another part of your body, such as your eyes. Do not touch the sores or fluids to avoid spreading herpes to another part of your body. If you touch the sores or fluids, immediately wash your hands thoroughly to help avoid spreading your infection.

Some people who get genital herpes have concerns about how it will impact their overall health, sex life, and relationships. It is best for you to talk to a health care provider about those concerns, but it also is important to recognize that while herpes is not curable, it can be managed. Since a genital herpes diagnosis may affect how you will feel about current or future sexual relationships, it is important to understand how to talk to sexual partners about STDs. You can find one resource here: GYT Campaign, <http://npin.cdc.gov/stdawareness/>

If you are pregnant, there can be problems for you and your unborn child. See "I'm pregnant. How could genital herpes affect my baby?" above for information about this.

### **Can I still have sex if I have herpes?**

If you have herpes, you should tell your sex partner(s) and let him or her know that you do and the risk involved. Using condoms may help lower this risk but it will not get rid of the risk completely. Having sores or other symptoms of herpes can increase your risk of spreading the disease. Even if you do not have any symptoms, you can still infect your sex partners.

### **What is the link between genital herpes and HIV?**

Genital herpes can cause sores or breaks in the skin or lining of the mouth, vagina, and rectum. The genital sores caused by herpes can bleed easily. When the sores come into contact with the mouth, vagina, or rectum during sex, they increase the risk of giving or getting HIV if you or your partner has HIV.



### **Where can I get more information?**

Division of STD Prevention (DSTD)  
Centers for Disease Control and Prevention

[www.cdc.gov/std](http://www.cdc.gov/std)

Personal health inquiries and information about STDs:  
CDC-INFO Contact Center  
1-800-CDC-INFO (1-800-232-4636)  
Contact <https://www.cdc.gov/dcs/ContactUs/Form>

### **Resources:**

CDC National Prevention Information Network (NPIN)  
<https://npin.cdc.gov/disease/stds>  
P.O. Box 6003  
Rockville, MD 20849-6003  
E-mail: npin-info@cdc.gov

American Sexual Health Association (ASHA)  
<http://www.ashasexualhealth.org/stdsstis/>  
P.O. Box 13827  
Research Triangle Park, NC 27709-3827  
1-800-783-9877

# PREVENTING HIV TRANSMISSION

**Undetectable = Untransmittable (U=U)**  
for Health Professionals

## What is U=U?

### Undetectable = Untransmittable (U=U)

communicates the scientific consensus that HIV cannot be sexually transmitted when a person living with HIV takes and adheres to antiretroviral therapy (ART) and maintains a viral load of less than 200 copies/ml (measured every 4-6 months).<sup>1,2,3,4,5,6</sup>



### KEY FACTS



Regular viral load testing every 4 to 6 months is the only way to know if an individual has reached and maintained viral suppression.



Condoms or pre-exposure prophylaxis (PrEP) are not needed to prevent HIV transmission when a person is virally suppressed. Condoms are still best practice to prevent other sexually transmitted infections or unwanted pregnancy.



U=U applies only to sexual transmission. It does not apply to sharing drug use equipment, or during pregnancy, breastfeeding, or chestfeeding.



A person with a low amount of HIV is not cured of HIV. However, people who take their HIV treatment consistently can live a long healthy life.



HIV antiretroviral medication coverage differs by province and territory. For more information, see a Summary: HIV antiretroviral medication coverage in Canada.

### KEY TERMS

#### Viral load

The amount of HIV in the blood.

#### Viral suppression

A viral load less than 200 copies/ml of blood with consecutive measurements every 4 to 6 months.

#### Undetectable

A viral load that cannot be detected by standard tests. The specific threshold for what is considered “undetectable” may vary depending on the type of test. When referring to U=U, viral suppression and undetectable are used synonymously.

#### Untransmittable

HIV cannot be transmitted sexually when a person achieves viral suppression (or has an undetectable viral load).



Public Health  
Agency of Canada

Agence de la santé  
publique du Canada

Canada

# PREVENTING HIV TRANSMISSION

**Undetectable = Untransmittable (U=U)**  
for Health Professionals

## Make U=U part of your practice

Integrating U=U into routine HIV care has several benefits...



### Improved health and well-being

When patients know about U=U, they are more likely to initiate and adhere to treatment, which leads to better health outcomes.



### Preventing transmission

Effective treatment prevents HIV from being passed on and reduces new infections.



### Improved patient relationships and reduced stigma

Discussing U=U as part of regular sexual health messaging can help change the way people think and talk about HIV by enabling conversations about sex without fear or shame.



### Empowerment

U=U empowers people living with HIV to have control of their well-being and make informed choices about their sexual health.

For more information, visit [Canada.ca/HIV](https://Canada.ca/HIV).

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# Biomedical prevention of HIV

## HIV PrEP and HIV PEP

	HIV Pre-exposure prophylaxis (PrEP)	HIV Post-exposure prophylaxis (PEP)
What are PrEP and PEP?	<p>HIV PrEP involves taking oral or injectable antiretroviral medications on an <b>ongoing basis</b> to prevent an HIV infection.</p> <p>Intended for regular use as an ongoing HIV prevention method.</p>	<p>HIV PEP involves taking oral antiretroviral medications as soon as possible <b>after a high-risk exposure</b> to prevent an HIV infection.</p> <p>Intended to prevent HIV transmission from a singular exposure.</p>
When is it taken?	<p>HIV PrEP is taken both <b>before and after</b> exposures that carry a high risk of HIV.</p> <p>Oral HIV PrEP involves taking a pill once a day, on an ongoing basis.</p> <p>Long-acting injectable PrEP is first given as two initiation injections one month apart, followed by an injection every two months thereafter.</p>	<p>HIV PEP should be started as soon as possible <b>after</b> a high-risk exposure to HIV, up to a maximum of 72 hours afterwards.</p> <p>HIV PEP involves taking oral pills daily for 4 weeks (28 days).</p> <p>HIV PEP can be taken on more than one occasion, if needed. However, individuals who have taken HIV PEP and are at ongoing risk of HIV exposure should consider taking HIV PrEP.</p>
Who should be considered for PrEP and PEP?	<p>HIV PrEP should be considered for individuals who do not have HIV and who participate in activities that have increased risk of exposure to HIV.*</p> <p>Some sexual activities that have increased risk of HIV, including sex with:</p> <ul style="list-style-type: none"><li>➢ no or inconsistent condom use; or</li><li>➢ a partner(s) whose HIV status is unknown; or</li><li>➢ a partner(s) who is living with HIV and who is <b>not</b> on treatment**; or</li><li>➢ the use of drugs or alcohol; or</li><li>➢ the exchange for drugs or money.</li></ul> <p>Sharing drug use equipment is high risk for HIV.</p> <p>A history of other sexually transmitted and blood-borne infections (STBBI) is a risk factor for HIV.</p>	<p>HIV PEP should be considered for individuals who do not have HIV and who have had a high-risk exposure to HIV.</p> <p>A high-risk exposure could occur in a work context</p> <ul style="list-style-type: none"><li>➢ e.g., exposure to blood or bodily fluids in a healthcare setting</li></ul> <p>Some sexual activities are high risk for HIV exposure</p> <ul style="list-style-type: none"><li>➢ e.g., condomless sex with a partner who is living with HIV and who is not on treatment**</li></ul> <p>HIV PEP may be recommended after a sexual assault.</p>

\* The listed criteria can be used to identify people who may benefit from HIV PrEP, but is not exhaustive. It is reasonable to prescribe HIV PrEP to adults/adolescents who request it as some people may not feel comfortable disclosing their sexual or drug use behaviours to a healthcare provider.

\*\* HIV is not passed on through sex when a person living with HIV is on treatment and the amount of HIV in their blood remains very low (the viral load is maintained at less than 200 copies/ml measured every 4 to 6 months).



# Other considerations

- › HIV PrEP and HIV PEP do not prevent other STBBI.
- › HIV PrEP and HIV PEP are highly effective when they are taken as prescribed.
- › "On demand" HIV PrEP may be an alternative for gay, bisexual and other men who have sex with men (gbMSM) to prevent HIV through sexual activity. This involves taking 2 pills of a certain antiretroviral medication 2-24 hours before a first high risk sexual exposure, followed by one pill daily until 48 hours after the last exposure.
- › Taking HIV PrEP involves initial testing, including testing for HIV and other STBBI, and seeing a healthcare provider every 3 months for clinical evaluation and HIV and STBBI testing.
- › Consult your drug benefits plan or provincial/territorial HIV programs for more information on coverage of HIV PrEP and HIV PEP through private or provincial/territorial drug formularies.

For information on prescribing, please refer to the **Canadian Guideline on HIV Pre-exposure Prophylaxis and Post-exposure Prophylaxis**

# Trichomoniasis - CDC Fact Sheet



## What is trichomoniasis?

Trichomoniasis (or “trich”) is a very common sexually transmitted disease (STD) that is caused by infection with a protozoan parasite called *Trichomonas vaginalis*. Although symptoms of the disease vary, most women and men who have the parasite cannot tell they are infected.

## How common is trichomoniasis?

Trichomoniasis is considered the most common curable STD. In the United States, an estimated 3.7 million people have the infection, but only about 30% develop any symptoms of trichomoniasis. Infection is more common in women than in men, and older women are more likely than younger women to have been infected.

## How do people get trichomoniasis?

The parasite is passed from an infected person to an uninfected person during sex. In women, the most commonly infected part of the body is the lower genital tract (vulva, vagina, or urethra), and in men, the most commonly infected body part is the inside of the penis (urethra). During sex, the parasite is usually transmitted from a penis to a vagina, or from a vagina to a penis, but it can also be passed from a vagina to another vagina. It is not common for the parasite to infect other body parts, like the hands, mouth, or anus. It is unclear why some people with the infection get symptoms while others do not, but it probably depends on factors like the person’s age and overall health. Infected people without symptoms can still pass the infection on to others.

## What are the signs and symptoms of trichomoniasis?

About 70% of infected people do not have any signs or symptoms. When trichomoniasis does cause symptoms, they can range from mild irritation to severe inflammation. Some people with symptoms get them within 5 to 28 days after being infected, but others do not develop symptoms until much later. Symptoms can come and go.

Men with trichomoniasis may feel itching or irritation inside the penis, burning after urination or ejaculation, or some discharge from the penis.

Women with trichomoniasis may notice itching, burning, redness or soreness of the genitals, discomfort with urination, or a thin discharge with an unusual smell that can be clear, white, yellowish, or greenish.

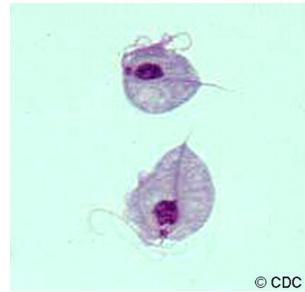
Having trichomoniasis can make it feel unpleasant to have sex. Without treatment, the infection can last for months or even years.

## What are the complications of trichomoniasis?

Trichomoniasis can increase the risk of getting or spreading other sexually transmitted infections. For example, trichomoniasis can cause genital inflammation that makes it easier to get infected with the HIV virus, or to pass the HIV virus on to a sex partner.

## How does trichomoniasis affect a pregnant woman and her baby?

Pregnant women with trichomoniasis are more likely to have their babies too early (preterm delivery). Also, babies born to infected mothers are more likely to have an officially low birth weight (less than 5.5 pounds).



© CDC  
Two *Trichomonas vaginalis* parasites, magnified (seen under a microscope)

## How is trichomoniasis diagnosed?

It is not possible to diagnose trichomoniasis based on symptoms alone. For both men and women, your primary care doctor or another trusted health care provider must do a check and a laboratory test to diagnose trichomoniasis.

## What is the treatment for trichomoniasis?

Trichomoniasis can be cured with a single dose of prescription antibiotic medication (either metronidazole or tinidazole), pills which can be taken by mouth. It is okay for pregnant women to take this medication. Some people who drink alcohol within 24 hours after taking this kind of antibiotic can have uncomfortable side effects.

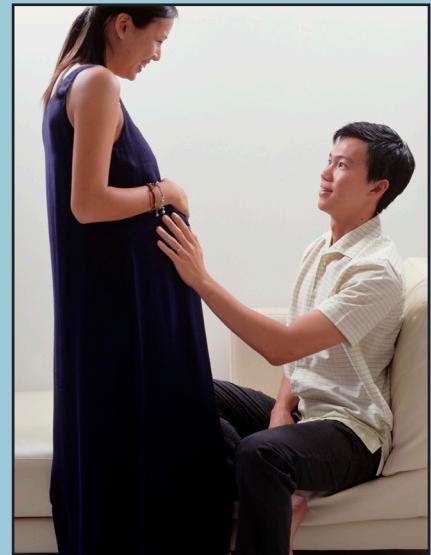
People who have been treated for trichomoniasis can get it again. About 1 in 5 people get infected again within 3 months after treatment. To avoid getting reinfected, make sure that all of your sex partners get treated too, and wait to have sex again until all of your symptoms go away (about a week). Get checked again if your symptoms come back.

## How can trichomoniasis be prevented?

Using latex condoms correctly every time you have sex will help reduce the risk of getting or spreading trichomoniasis. However, condoms don't cover everything, and it is possible to get or spread this infection even when using a condom.

The only sure way to prevent sexually transmitted infections is to avoid having sex entirely. Another approach is to talk about these kinds of infections before you have sex with a new partner, so that you can make informed choices about the level of risk you are comfortable taking with your sex life.

If you or someone you know has questions about trichomoniasis or any other STD, especially with symptoms like unusual discharge, burning during urination, or a sore in the genital area, check in with a health care provider and get some answers.



## Where can I get more information?

Division of STD Prevention (DSTD)  
Centers for Disease Control and Prevention  
[www.cdc.gov/std](http://www.cdc.gov/std)

CDC-INFO Contact Center  
1-800-CDC-INFO (1-800-232-4636)  
Email: [cdcinfo@cdc.gov](mailto:cdcinfo@cdc.gov)

## Resources

CDC National Prevention Information  
(NPIN)  
P.O. Box 6003  
Rockville, MD 20849-6003  
E-mail: [info@cdcnpin.org](mailto:info@cdcnpin.org)  
[www.cdcnpin.org](http://www.cdcnpin.org)

American Sexual Health Association  
(ASHA)  
P. O. Box 13827  
Research Triangle Park, NC 27709-3827  
1-800-783-9877  
[www.ashastd.org](http://www.ashastd.org)

## Effectiveness of condoms in preventing sexually transmitted infections

King K. Holmes,<sup>1</sup> Ruth Levine,<sup>2</sup> & Marcia Weaver<sup>3</sup>

**Abstract** In June 2000, the United States National Institutes of Health (NIH) organized a review of the scientific evidence on the effectiveness of condoms in preventing sexually transmitted infections (STIs). The review concluded that condoms were effective in protecting against transmission of HIV to women and men and in reducing the risk of men becoming infected with gonorrhoea. Evidence for the effectiveness of condoms in preventing other STIs was considered to be insufficient. We review the findings of prospective studies published after June 2000 that evaluated the effectiveness of condoms in preventing STIs. We searched Medline for publications in English and included other articles, reports, and abstracts of which we were aware. These prospective studies, published since June 2000, show that condom use is associated with statistically significant protection of men and women against several other types of STIs, including chlamydial infection, gonorrhoea, herpes simplex virus type 2, and syphilis. Condoms may also be associated with protecting women against trichomoniasis. While no published prospective study has found protection against genital human papillomavirus (HPV) infection, two studies reported that condom use was associated with higher rates of regression of cervical intraepithelial neoplasia and clearance of cervical HPV infection in women and with regression of HPV-associated penile lesions in men. Research findings available since the NIH review add considerably to the evidence of the effectiveness of condoms against STIs. Although condoms are not 100% effective, partial protection can substantially reduce the spread of STIs within populations.

**Keywords** Condoms/utilization; Sexually transmitted diseases/prevention and control; Herpes genitalis/prevention and control; Gonorrhoea/prevention and control; Chlamydia infections/prevention and control; Trichomonas vaginitis/prevention and control; Syphilis/prevention and control; Papillomavirus, Human; Prospective studies; Review literature (*source: MeSH, NLM*).

**Mots clés** Condom/utilisation; Maladies sexuellement transmissibles/prévention et contrôle; Herpès génital/prévention et contrôle; Gonococcie/prévention et contrôle; Chlamydia, Infection/prévention et contrôle; Vaginite trichomonas/prévention et contrôle; Syphilis/prévention et contrôle; Papillomavirus humain; Etude prospective; Revue de la littérature (*source: MeSH, INSERM*).

**Palabras clave** Condones/utilización; Enfermedades sexualmente transmisibles/prevención y control; Herpes genital/prevención y control; Gonorrea/prevención y control; Infecciones por chlamydia/prevención y control; Vaginitis por trichomonas/prevención y control; Sífilis/prevención y control; Papilomavirus humano; Estudios prospectivos; Literatura de revisión (*fuente: DeCS, BIREME*).

**الكلمات المفتاحية:** استخدام العوازل الذكرية؛ الوقاية من الأمراض المنقوله جنسياً ومكافحتها؛ الوقاية من الهرس التناصلي ومكافحته؛ الوقاية من داء السيلان ومكافحته؛ الوقاية من عدوى المثلثات ومكافحتها؛ الوقاية من التهاب المهبل بالمشعرات ومكافحته؛ الوقاية من الزهري ومكافحته؛ فيروس الورم الحليمي البشري؛ الدراسات الاستباقية؛ مراجعة الدراسات المشورة. (*المصدر: رؤوس الموضوعات الطبية- المكتب الإقليمي لشرق المتوسط*).

Bulletin of the World Health Organization 2004;82:454-461.

Voir page 459 le résumé en français. En la página 460 figura un resumen en español.

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### Introduction

In June 2000, the United States National Institutes of Health (NIH), in collaboration with the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration and the United States Agency for International Development (USAID), convened an expert panel to evaluate peer-reviewed published studies on the effectiveness of latex condoms used by men (male latex condoms) in preventing sexually transmitted infections

(STIs) during vaginal intercourse (1). The NIH defines condom effectiveness as “the level of protection against STDs (sexually transmitted diseases) when condoms are used consistently and correctly” (1).

The review looked at HIV infection, gonorrhoea, chlamydial infection, syphilis, chancroid, trichomoniasis, genital herpes and genital human papillomavirus (HPV) infection. The panel of 28 researchers excluded papers with flawed study designs or methods.

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Based on the results of the remaining prospective studies, the panel reached three key conclusions. First, consistent condom use (i.e., using condoms during every act of vaginal intercourse) among heterosexual couples in which one partner was infected with HIV reduced the risk of HIV transmission from men to women and vice versa. This finding was based on a meta-analysis of condom effectiveness studies by Davis & Weller (2). They estimated that compared with no condom use, consistent condom use resulted in an overall 87% reduction in risk of HIV transmission, with the best-case and worst-case scenarios ranging from 60% to 96%. In an update of this analysis, Weller & Davis reported a revised estimate of an 80% reduction in risk with a range of 35–94% (3).

Second, the NIH report concluded that consistent condom use may reduce the risk of gonorrhoea in men. This finding was based on a 1978 report by Hooper et al. (4), which was a prospective study of the risk of transmission of gonorrhoea to men in the United States Navy from a pool of women with a known prevalence of gonorrhoea. A subsequent reanalysis of those data showed that condoms provided a statistically significant level of protection against the combined outcome of gonorrhoea or nongonococcal urethritis in exposed men (5).

Third, due to insufficient evidence from prospective studies, the reviewers were unable to determine the effectiveness of condoms in preventing gonorrhoea and chlamydial infection in women, or in preventing syphilis, chancroid, trichomoniasis, genital herpes or genital HPV infection in men or women. The panel strongly cautioned the public against misinterpreting the scanty evidence. The small number of well designed prospective studies precluded the panel from making judgments about the effectiveness of condoms in preventing other STIs; the reviews stated that the lack of data were not to be construed as evidence either supporting or denying the effectiveness of condoms.

As the NIH prepared to release its report in July 2001, other health agencies responded to the pending report (6, 7). For example, the CDC reviewed its treatment guidelines for STIs that were issued in 2000, and in the same month that the NIH released its report, reasserted the protective value of condoms against STIs (7). WHO included condom programmes among the essential components of public health packages for preventing and controlling STIs in the most recent edition of the *Guidelines for the management of sexually transmitted infections* (8).

Since the NIH review, reports of several additional prospective studies have further addressed the effectiveness of condoms. A literature review by Hearst & Chen (9) considered several lines of evidence for the efficacy of condom use and other behavioural changes in preventing the sexual transmission of HIV; it also discussed related issues about HIV prevention programmes.

We examine findings that have become available since June 2000 from prospective studies of the effectiveness of male condoms in preventing STIs and briefly discuss the limitations of these studies and the effectiveness of programmes to promote condom use.

## Methods

We searched Medline for articles published in English after June 2000 with the keyword "effectiveness" and the MeSH heading "condom" and with the following three MeSH terms: "condoms", "evaluation studies", and "sexually transmitted

diseases". We reviewed the abstracts of the selected studies to identify prospective cohort studies. We also conducted a limited search for randomized controlled trials using the MeSH heading "condom" and the MeSH term "sexually transmitted diseases". In addition, we identified and reviewed other articles, reports and abstracts that we were aware of having been published, presented, or reported after June 2000.

## Findings

Point estimates and confidence intervals of prospective studies on the effectiveness of condom use in preventing STIs are presented in Fig. 1. A summary of the design and participants in those studies can be found in Table 1 (web version only, available at: <http://www.who.int/bulletin>).

### **Herpes simplex virus type 2**

Genital herpes, usually caused by infection with herpes simplex virus type 2 (HSV-2), is a chronic disease found throughout the world; in sub-Saharan Africa, the seroprevalence of HSV-2 is 70% or higher. Genital HSV infection is transmissible even when partners have no active genital symptoms or lesions.

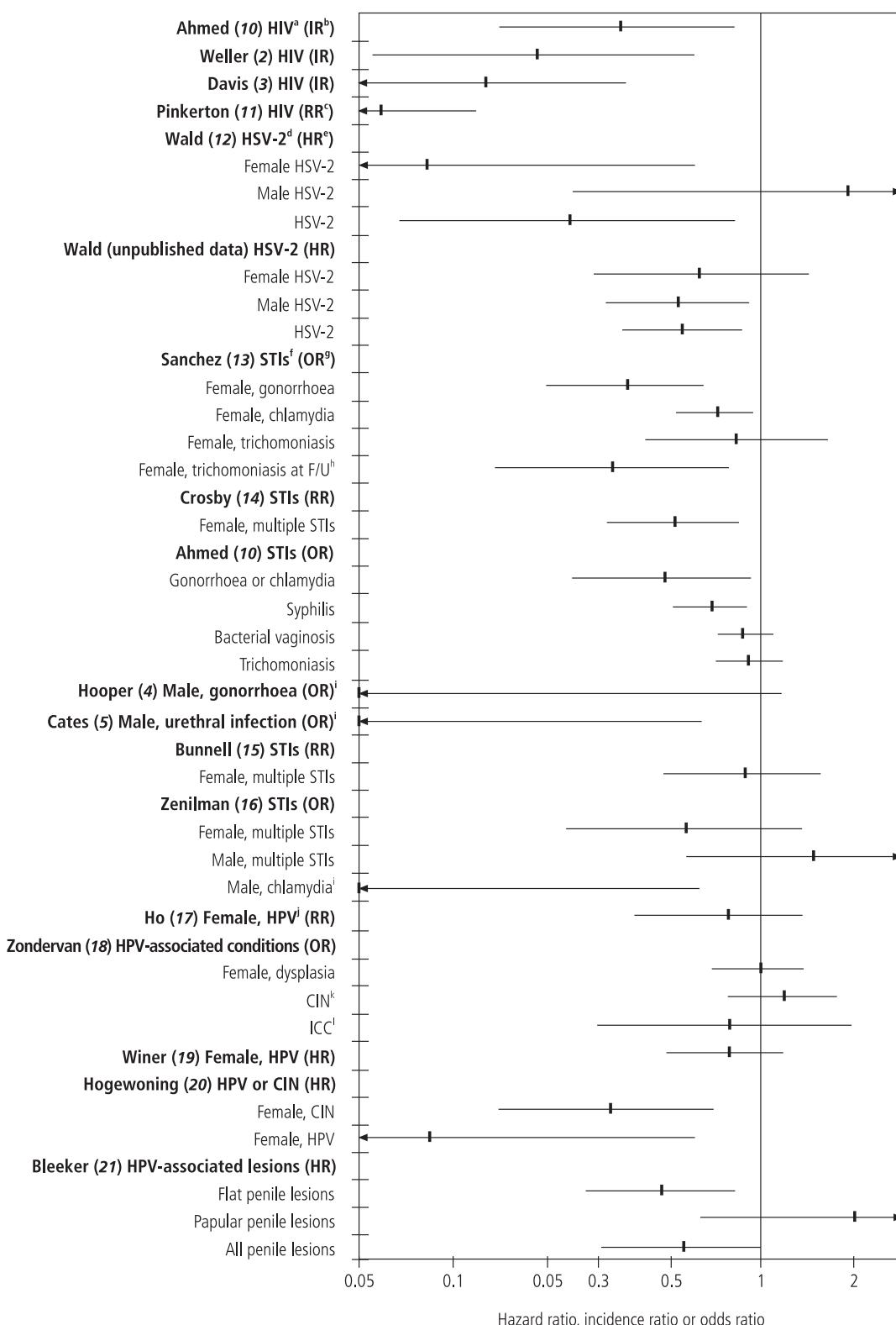
Prospective studies conducted in the United States have shown that condoms partially protect men and women against new infections with HSV-2 (12, A. Wald et al., unpublished data presented at the 2002 National STD Prevention Conference in San Diego, CA). In one study (12), Wald et al. analysed data from an HSV-2 candidate vaccine trial conducted in the mid-1990s that followed 528 monogamous, HSV-2-discordant couples (one partner was infected with HSV-2, the other was not) for 18 months. The median reported use of condoms was 25%; it was relatively low because the couples were monogamous. Using condoms during more than 25% of sex acts was associated with a 92% reduction in the risk of women acquiring HSV-2 but was not associated with a protective effect among men.

However, in a separate trial of this candidate vaccine among people with more than three sexual partners or at least one STI in the past year, Wald et al. found that the median reported use of condoms was 65%, and that using condoms during more than 65% of acts of vaginal or rectal penetration provided partial protection for men (A. Wald et al., unpublished data, presented at the 2002 National STD Prevention Conference in San Diego, CA). Nonetheless, HSV-2 infection was acquired, although rarely, even by people who reported using condoms during 100% of sexual activity.

### **Gonorrhoea, chlamydial infection, trichomoniasis and syphilis**

For the first time, Sanchez et al. (13) demonstrated the statistically significant effectiveness of condoms in preventing not only gonorrhoea, but also chlamydial infection and trichomoniasis in women. A cohort of 917 female sex workers in Lima, Peru, were re-examined monthly for STIs; they were also given condoms. During the observation period of 7908 person-months, the reported rate of consistent condom use rose by 20%. Compared with all others, those women who reported using condoms consistently since the previous examination had a 62% reduction in the risk of acquiring gonorrhoea and a 26% reduction in the risk of acquiring chlamydial infection. There was also evidence of a significant reduction in the risk of acquiring trichomoniasis.

Fig. 1. Effectiveness of condoms in preventing of sexually transmitted infections

<sup>a</sup>HIV = human immunodeficiency virus.<sup>b</sup>IR = incidence ratio.<sup>c</sup>RR = relative risk.<sup>d</sup>HSV-2 = herpes simplex virus type 2.<sup>e</sup>HR = hazard ratio.<sup>f</sup>STI = sexually transmitted infection.<sup>g</sup>OR = odds ratio.<sup>h</sup>F/U = follow-up.<sup>i</sup>The ORs for these studies were zero, and the lower boundary of the 97.5% CI was 0.<sup>j</sup>HPV = human papillomavirus.<sup>k</sup>CIN = cervical intraepithelial neoplasia.<sup>l</sup>ICC = invasive cervical cancer.

The bold vertical lines correspond to the point estimates, and the horizontal lines to the 95% confidence intervals.

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Macaluso et al. (unpublished report submitted to the US National Institute of Child Health and Human Development, 2000) found that among women considered to be at high-risk for STIs the consistent and correct use of latex male condoms or female condoms was associated with a statistically significant reduction in the combined incidence of gonorrhoea, chlamydial infection or syphilis in high-risk women when compared to rates of use of less than 50%. This prospective study followed female patients at STD clinics in the United States who had monthly STI tests for six months from 1995 to 1998.

Crosby et al. (14) reported that using condoms for 100% of sex acts was associated with a significant reduction in the combined incidence of gonorrhoea, chlamydial infection, or trichomoniasis among adolescent African-American females aged 14–18 years. In this study, the researchers tested for all three STIs and treated girls who were infected at baseline. Six months later, the 380 girls who reported penile–vaginal sex were retested and interviewed about condom use. Of the girls who reported using condoms each time they had had sex since baseline, 17.8% of them had at least one STI compared with 30% of the girls who did not report using condoms consistently (odds ratio (OR) = 1.85; 95% confidence interval (CI) = 1.13–3.04 after adjusting for STI at baseline and having more than one sex partner in the interim).

Ahmed et al. (10) analysed data from a community-based randomized controlled trial of mass treatment for STIs in rural Rakai, Uganda, from 1994 to 1998. HIV prevalence among the study population was 16%; the prevalence of syphilis was 10%, chlamydial infection was 3.1% and gonorrhoea was 1.5%. Of the 17 264 adult participants, only 4.4% reported consistently using condoms in the year prior to the study. During follow-up, for men and women combined, consistent condom use was associated with a significant reduction in the incidence of STIs when compared with the non-use of condoms. There was a significant reduction in the incidence of HIV (relative risk (RR) = 0.37; 95% CI = 0.15–0.88), a significant reduction in syphilis seroprevalence (OR = 0.71; 95% CI = 0.53–0.94) and a significant reduction in the prevalence of gonorrhoea, chlamydial infection, or both (OR = 0.50; 95% CI = 0.25–0.97). The prevalences of trichomoniasis and bacterial vaginosis among women were not reduced.

## Human papillomavirus infection

Manhart & Koutsky (22) evaluated the effectiveness of condoms in protecting against HPV infection and HPV-related conditions, such as genital warts and cervical cancer. A meta-analysis of 20 studies found no evidence that condoms were effective against genital HPV infection. Neither of the two prospective studies reviewed found that consistent condom use was effective in preventing genital HPV infection or HPV-related conditions. Subsequently, Winer et al. (19) followed 444 female students at university as part of a longitudinal study of the cumulative incidence of genital HPV infection. They found that consistently using condoms with a new partner was not associated with significant protection against HPV (hazard ratio (HR) = 0.8; 95% CI = 0.5–1.2). Data on condom breakage or vaginal penetration before condoms were put on were not collected, nor was the analysis adjusted for frequency of intercourse.

Dunne et al. reviewed the methods of 44 studies conducted between 1996 and 2001 that examined condom use, HPV infection, and HPV-related conditions (EF Dunne et al., unpublished data presented at the HPV Clinical Workshop and

20th International Papillomavirus Conference, Paris, 2002). They found that methodological limitations made it difficult to accurately assess condom effectiveness, and they called for studies to consider the consistency and correctness of condom use, incident infections, and the infection status of the partner in the design of studies.

In a unique clinical trial in the Netherlands, Hogewoning et al. (20) randomly allocated 135 women not regularly using condoms who had untreated cervical intraepithelial neoplasia (CIN) and their male partners either to use condoms or not use condoms for all instances of vaginal intercourse. Those couples randomized to use condoms had a significantly higher cumulative two-year rate of disease regression (53% versus 35%; HR = 3.1; 95% CI = 1.4–7.1) as well as a higher cumulative two-year rate of HPV clearance (23% versus 4%; HR = 12.1; 95% CI = 1.5–97.2).

Bleeker et al. (21) examined the male partners of the women in this study for the presence of penile lesions and for HPV using polymerase chain reaction testing of penile swabs. Consistent condom use over a minimum period of three months was associated with a reduction in the median time until clinical regression of all penile lesions (HR for regression = 1.8; 95% CI = 1.0–3.3; P = 0.05 by Cox regression analysis). Interpreting the findings of these two studies is not simple (20, 21). The authors suggest that transmission of HPV back and forth between partners during unprotected sex may prolong the duration of HPV infection, CIN, and penile lesions.

## Discussion

This review of prospective studies published since June 2000 has identified evidence that consistent condom use is associated not only with reduced transmission of HIV and with reduced acquisition of urethral infection among men, but also with:

- reduced acquisition of genital HSV-2 infection by men and women;
- reduced acquisition of syphilis by men and women;
- reduced acquisition of chlamydial infection by men and women;
- reduced acquisition of gonorrhoea by women
- possibly reduced acquisition of trichomoniasis infection by women;
- accelerated regression of cervical and penile HPV-associated lesions and accelerated clearance of genital HPV infection by women.

## Limitations of studies

Only in prospective studies can the temporal relationship between STIs and condom use be explored. Because many prospective studies have now shown that condom use reduces the transmission of HIV and several other STIs, randomized trials with a high-risk control group that doesn't use condoms have been viewed as unwarranted. Although many studies have randomly allocated people or samples to various prevention interventions that included the enhanced promotion of condom use, we believe the two studies of couples with HPV-related conditions (20, 21) are the only trials in which participants were randomly allocated to condom use or no condom use. The study was strengthened by randomization of couples rather than individuals, randomization to consistent condom use compared with no condom use, and by measurement of outcomes in male and female partners simultaneously.

Two methodological issues in observational studies of condom effectiveness are of particular concern: (1) underestimation of point estimates, and (2) exposure to infected partners.

Underestimates of condom effectiveness could result from over-reporting of condom use by participants in order to satisfy the interviewer (known as social desirability bias). Devine & Aral (23) conducted simulation experiments to illustrate that over-reporting of condom use reduced both the point estimate of condom effectiveness and the power of the study to detect a protective effect of condom use.

Studies that do not adjust for the improper use of condoms could also underestimate the effectiveness of proper use. (24) For example, in a retrospective study in the United States among 98 male university students selected because they had used condoms during vaginal intercourse at least five or more times, and at least once during the previous month, Warner et al. (24) found that in 13% of 270 instances, condoms broke or were used incorrectly; this allowed for direct penile–vaginal contact, and consequently, exposure to STIs.

Restricting condom effectiveness analyses to participants with known exposure to infected partners reduces confounding and provides a more accurate measurement of the protective effects of condoms against STIs. In a cross-sectional analysis of baseline data from Project RESPECT, Warner et al. (25) compared estimates of the effectiveness of condoms in a subsample of people with known exposure (they were referred to the clinic because their partner had gonorrhoea or chlamydial infection) with estimates in a subsample of people who visited the clinic for other reasons. Among the 429 participants with known exposure, the consistent use of condoms was associated with a significant reduction in those STIs ( $OR = 0.42$ ; 95% CI = 0.18–0.99). Among the 4314 participants for whom exposure information was not known, the consistent use of condoms was less effective ( $OR = 0.82$ ; 95% CI = 0.66–1.01).

Fitch et al. (26) note the importance of differentiating between effectiveness in single-episode use and “period effectiveness”. The latter measure takes into account user error, condom failure, the variable infectiousness of particular STIs, and the impact of repeated exposure. Also, it has proven far more feasible to promote condom use during occasional acts of commercial or casual sex than to introduce and sustain consistent condom use during repeated acts of intercourse over years among stable couples (9).

Crosby et al. (27) identified several potential problems and solutions in condom effectiveness studies.

- An infection-free cohort should be established at baseline through testing and treatment of nonviral STIs.
- It is essential to have sample sizes that are adequate to detect a significant impact of condom use.
- Using the number of unprotected sex acts is preferable to calculating the percentage of times that a condom is used, as the latter does not account for variation in frequency of intercourse.

In view of these issues, it seems remarkable that data from longitudinal studies and the one randomized trial as well as several cross-sectional or case–control studies have nonetheless demonstrated the statistically significant effectiveness of condoms in protecting against HIV and most of the other STIs examined.

Not all earlier prospective observational studies found that consistent condom use was associated with a decreased risk of STIs. For example, Bunnell et al. (15) followed 484 adolescents at four clinics over a six-month period and found

an incident STI in 21% of 61 participants reporting 100% condom use and in 23% of 423 adolescents reporting inconsistent use or no condom use. Zenilman et al. (16) prospectively studied condom use among 598 male and female patients at an STD clinic in Baltimore, Maryland. During follow-up STI incidence was similar for participants reporting 100% condom use and for those reporting that they never used condoms; this was found for both male and female patients. However, when specific STI incidence was examined rather than combined STI incidence, consistent condom use (as compared with sometime use or never use) was associated with a significantly lower rate of chlamydial infection in men (1, 16).

## Recommendations for further research

Future research using improved methods for ascertaining the consistency, correctness, and selectivity of condom use may lead to better point estimates of effectiveness. In future trials the accurate assessment of condom use will help delineate the causal pathway linkage of the effectiveness of STI prevention methods that do or do not include the promotion of condom use (28).

The general quality of research on condom effectiveness in preventing HIV and other STIs can be readily improved by routinely collecting the partner-specific data in relation to testing for current STIs or incident HIV infection. Questions that should be asked include:

- How many times did you have sex with a particular partner during the past month? How many times were condoms not used with that partner during the past month?
- How many times in the past month were condoms put on after the start of intercourse? How many times were condoms removed before stopping intercourse? How many times did condoms slip off or break before intercourse ended?
- How many times has a particular partner had an STI in the past month? What type(s) of STI(s)?
- Has that particular partner had other partners during the past month?

Condom use is typically more common with partners perceived as likely to be infected than with those not perceived as likely to be infected. Collecting similar data for the past three-month period or longer would also be useful, depending on which STI is being studied. Such information would contribute to research on condom effectiveness and would strengthen monitoring and evaluation processes.

## The effectiveness of condom-promotion programmes

The question remains whether programmes designed to increase the frequency of condom use actually achieve increased use and whether they decrease the individual's risk of acquiring HIV and other STIs. Many studies have shown that condom-promotion interventions decrease self-reports of unprotected sex, but fewer have examined the impact of such programmes on the actual incidence of STIs, including HIV infection. Fewer still have done so in randomized controlled trials in which participants were followed prospectively and specifically offered STI testing. Four individual-level or group-level randomized controlled trials that have included condom promotion have reported a reduced risk of STIs (29–31) (CB Boyer et al., unpublished data presented at the 15th Biennial Congress of the International Society for Sexually Transmitted Diseases Research, Ottawa, 2003).

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Project RESPECT, a multisite, individual-level randomized controlled trial involving 5700 heterosexual, HIV-negative patients at public STI clinics in the United States found that interactive, client-centred HIV and STI risk reduction counselling that emphasized avoiding unprotected sex resulted in more frequent reports of 100% condom use and a statistically significant 20% lower incidence of STIs over 12 months of follow-up when compared with counselling that used only didactic prevention messages (29).

In a group-level randomized trial, Shain et al. (30) found that enhanced counselling, which included three intensive, small-group sessions for female Hispanic and African-American patients at an STI clinic resulted in a lower incidence of gonorrhoea and chlamydial infection over the following year when compared with standard counselling. The sessions were based on ethnographic research; the sessions for Hispanic women were similar to those for African-American women, but there were some differences in emphasis. The effect of the intervention appeared to be mediated by a number of behavioural changes including increased condom use (32). Two other group-level randomized trials involving women also showed efficacy in preventing STIs (31, CB Boyer et al. unpublished data).

A randomized trial of voluntary HIV testing and counseling in Kenya, the United Republic of Tanzania and Trinidad between 1995 and 1998 (33), which was modelled on the Project RESPECT intervention, compared client-centred counselling with giving health information alone. It found there was a decrease in the incidence of unprotected intercourse with non-regular partners among those who had counselling. There was also a reduction of about 20% in new STIs which was similar to that seen in Project RESPECT but not statistically significant in this underpowered study.

In a field trial in Thailand involving nonrandomized but comparable groups of army conscripts, Celentano et al. (34) found that groups participating in a multicomponent HIV and STI prevention intervention that lasted for several months and contained a condom promotion component had 80% fewer incident STIs when compared with the control groups.

Finally, a London-based group-randomized trial of a one-day cognitive behavioural intervention designed to reduce STI incidence among men who have sex with men had different results (35). The intervention group reported a modest decrease in the incidence of unprotected anal intercourse but actually experienced a significantly increased risk of new STIs in comparison with the control group. This study illustrates the importance of measuring objective STI outcomes rather than relying only on self-reported changes in behaviour.

Thus, as with prospective studies of condom efficacy, not all harm-reduction interventions that include condom promotion have succeeded in reducing STI morbidity. Success undoubtedly depends on the intervention and the context, among other factors. Nonetheless, adequately powered studies (i.e., those having large enough sample sizes) that examined heterosexual populations have consistently shown a significant impact on subsequent STI outcomes when such outcomes have been measured.

## Conclusions

Since 2000 important new evidence (from prospective observational studies, one couple-randomized trial and additional multicomponent STI prevention trials that included condom-promotion components) has come to light to support the effectiveness of condoms in preventing STIs in men and women. In no study has the effectiveness been 100%. Nonetheless, even partially effective interventions can have a major impact on controlling the spread of STIs in the population (36). Balanced STI and HIV prevention programmes should include condom promotion along with a complementary combination of prevention strategies targeted towards different age groups, life stages, epidemic levels, and settings (37, 38). Condom promotion represents an important component of comprehensive HIV-prevention and STI-prevention strategies. ■

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## Résumé

### Efficacité du préservatif pour la prévention des infections sexuellement transmissibles

En juin 2000, les National Institutes of Health (NIH) des Etats-Unis d'Amérique ont organisé une revue des preuves scientifiques de l'efficacité du préservatif pour la prévention des infections sexuellement transmissibles (IST). Cet examen a permis de conclure que le préservatif était efficace pour la prévention de la transmission du VIH chez l'homme comme chez la femme et pour réduire le risque d'infection gonococcique chez l'homme. Les preuves de son efficacité pour la prévention des autres IST ont été jugées insuffisantes. Nous avons examiné les résultats d'études prospectives publiées après juin 2000 et portant sur

l'efficacité des préservatifs pour la prévention des IST. Nous avons recherché sur Medline les publications en anglais et y avons ajouté d'autres articles, rapports et sommaires dont nous avions connaissance. Ces études prospectives publiées depuis juin 2000 montrent que l'utilisation du préservatif est associée à une protection statistiquement significative, chez l'homme comme chez la femme, contre plusieurs autres types d'IST, dont les infections à Chlamydia, les gonococcies, les infections par le virus de l'herpès humain type 2 et la syphilis. Elle peut également être associée à une protection contre la trichomonase chez la

femme. Bien qu'aucune étude prospective publiée n'ait montré de protection contre l'infection génitale par le papillomavirus humain (PVH), deux études ont rapporté un taux plus élevé de régression des néoplasies intraépithéliales du col de l'utérus et de disparition des infections cervicales par le PVH chez la femme en cas d'utilisation du préservatif, et une régression des lésions du

pénis associées au PVH chez l'homme. Les résultats des travaux effectués depuis la revue des NIH ajoutent considérablement aux preuves de l'efficacité du préservatif contre les IST. Bien que les préservatifs ne soient pas efficaces à 100 %, la protection partielle qu'ils confèrent peut réduire sensiblement la propagation des IST dans les populations.

## Resumen

### Eficacia del preservativo como medio de prevención de las infecciones de transmisión sexual

En junio de 2000, los Institutos Nacionales de Salud (NIH) de los Estados Unidos organizaron una revisión de la evidencia científica disponible sobre la eficacia de los preservativos como medio de prevención de las infecciones de transmisión sexual (ITS). El estudio concluyó que los preservativos protegían eficazmente contra el VIH a hombres y mujeres y reducían el riesgo de que los hombres contrajeran gonorrea. No obstante, se consideró insuficiente la evidencia sobre la eficacia del preservativo como medio de prevención de otras ITS. Hemos examinado aquí los resultados de estudios prospectivos publicados con posterioridad a junio de 2000 en los que se evaluó la eficacia de los preservativos como método de prevención de las ITS. Buscamos en MEDLINE publicaciones en inglés, y añadimos otros artículos, informes y resúmenes que conocíamos. Estos estudios prospectivos, publicados después de junio de 2000, revelan que el uso de preservativos se asocia a una protección estadísticamente significativa de hombres y mujeres

frente a otros varios tipos de ITS, incluidas las infecciones por clamidias, la gonorrea, el virus herpes simple tipo 2 y la sifilis. Los preservativos también pueden proteger a las mujeres contra la tricomoniase. Si bien ninguno de los estudios prospectivos publicados ha revelado un efecto de protección contra la infección por el papilomavirus humano (VPH), en dos estudios se observó que el uso del preservativo se asociaba a mayores tasas de regresión de las neoplasias intraepiteliales cervicouterinas y de desaparición de la infección cervicouterina por VPH en las mujeres, así como de regresión de las lesiones de pene por VPH en los hombres. Los resultados de investigación aparecidos después de la revisión de los NIH refuerzan considerablemente la evidencia acumulada sobre la eficacia de los preservativos contra las ITS. Aunque los preservativos no son eficaces al 100%, la protección parcial conseguida puede reducir sustancialmente la propagación de las ITS en las poblaciones.

## ملخص

### فعالية العازل الذكري في الوقاية من العدوى المنقولة جنسياً

أُنْهَاطَ مِنَ الْعَدَوَىِ الْمُنْقُولَةِ جِنْسِيًّا، تَشْمِلُ الْعَدَوَىِ بِالْمُنْتَدِرَاتِ، وَالسِّيلَانِ، وَالنَّمَطِ الثَّانِي مِنْ فِيُوْرُوسِ الْهُرْبِيسِ الْبِسِيطِ، وَالْزَّهْرِيِّ. وَقَدْ تُؤَدِّيِ الْعَازِلُ الذَّكْرِيُّ أَيْضًاً إِلَىِ حِمَايَةِ النِّسَاءِ مِنْ دَاءِ الشَّعَرَاتِ. وَفِي حِينِ لَمْ تُشَرِّكِيْدَةِ اسْتَبِاقِيَّةٍ مُنْشَوَّرَةٍ إِلَىِ أَنَّ الْعَازِلُ الذَّكْرِيُّ تَقِيِّدَ مِنْ الْعَدَوَىِ بِفِيُوْرُوسِ الْوَرْمِ الْحَلِيمِيِّ التَّنَاسُليِّ الْبَشَرِيِّ، أَشَارَتْ دَرَاسَاتٌ إِلَىِ أَنَّ اسْتِخْدَامَ الْعَازِلِ الذَّكْرِيِّ يُؤَدِّيُ إِلَىِ مُعَدَّلَاتٍ تَرَاجِعِ عَالِيَّةٍ لِتَكُونُ الْوَرْمِ دَاخِلِ الظَّهَارَةِ فِي عَنْقِ الرَّحْمِ وَإِلَىِ الْوَقَايَةِ مِنَ الْعَدَوَىِ بِفِيُوْرُوسِ الْوَرْمِ الْحَلِيمِيِّ الْبَشَرِيِّ فِي النِّسَاءِ، وَإِلَىِ تَرَاجِعِ حَدَوثِ الْآَفَاتِ الْقَضْبِيَّةِ الْمَاصِحَّةِ لِلْعَدَوَىِ بِفِيُوْرُوسِ الْوَرْمِ الْحَلِيمِيِّ الْبَشَرِيِّ بَيْنِ الرِّجَالِ. وَتَوَفَّرُ نَتَائِجُ الْبَحْثِ، الَّتِي أَحْرَيَتْ بَعْدَ الدَّرَاسَةِ الَّتِي قَامَتْ بِهَا الْمَعَاهِدُ الصَّحِيفَةُ الْوَطَنِيَّةُ فِي الْوَلَيَاتِ الْمُتَّحِدةِ، بِيَنِّيَّاتٍ قَوِيَّةٍ عَلَىِ فَعَالِيَةِ الْعَازِلِ الذَّكْرِيِّ فِي الْوَقَايَةِ مِنَ الْعَادَوَىِ الْمُنْقُولَةِ جِنْسِيًّا. وَبَالرَّغْمِ مِنَ أَنَّ الْعَازِلِ الذَّكْرِيِّ لَيَسِّتُ فَعَالَةً بَنِيَّةً ۱۰۰٪، إِلَّا أَنَّ مَا تَحْقِقَهُ مِنْ وَقاِيَةٍ جَزِئِيَّةٍ مِنَ الْمُمْكِنِ أَنْ تَحدِّدَ بِشَكَلٍ مَلْمُوسٍ مِنَ انتِشارِ الْعَادَوَىِ الْمُنْقُولَةِ جِنْسِيًّا بَيْنِ السِّكَانِ.

**ملخص :** نظمت المعاهد الصحية الوطنية في الولايات المتحدة ، في حزيران/يونيو ۲۰۰۰ ، دراسة لمراجعة البيانات العلمية حول فعالية العازل الذكري في الوقاية من العدوى المنقولة جنسياً . وخلصت الدراسة إلى فعالية العازل الذكري في الوقاية من انتقال فيروس الإيدز إلى النساء والرجال ، وفي المهد من مخاطر إصابة الرجال بداء السيلان . ولم تتوصل الدراسة إلى بيانات كافية على فعالية العازل الذكري في الوقاية من سائر العدواوى المنقولة جنسياً . وتم في إطار هذه الدراسة مراجعة نتائج الدراسات الاستباقية التي نُشرت بعد حزيران/يونيو ۲۰۰۰ والتي قَيَّمت فعالية العازل في الوقاية من العدواوى المنقولة جنسياً . وقمنا أيضاً في إطار هذه الدراسة بالبحث في شبكة استرجاع النشريات الطبية Medline عن البحوث المنشورة باللغة الإنجليزية ، إضافة إلى الاطلاع على المقالات والتقارير وملخصات البحوث المتاحة لدينا . وتبين هذه الدراسات الاستباقية ، التي نُشرت بعد حزيران/يونيو ۲۰۰۰ ، أنَّ استخدام العازل الذكري يؤدي إلى حماية ذات أهمية إحصائية للرجال والنساء من عدة

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Table 1. Summary of prospective studies on effectiveness of condom use in preventing sexually transmitted diseases published or presented since June 2000 compared with studies cited in National Institutes of Health review (1)

Study	Design	Participants	Definition of condom use	Notes on estimates
<b>HIV<sup>a</sup> studies</b>				
Ahmed et al. 2001 (10)	Community-based randomized trial of mass treatment for STIs in rural Rakai, Uganda, with follow-up every 10 months for 30 months	9536 women and 7728 men aged 15–59 years in 56 communities	Consistent condom use versus never use	Poisson regression model with covariates for demographic characteristics and behavioural risk
Weller & Davis 2004 (3)	Meta-analysis of condom effectiveness in reducing heterosexual transmission based on studies in several countries	14 longitudinal studies of serodiscordant couples	Consistent condom use versus never use	Point estimate is the IRR <sup>f</sup> of always-users in 13 studies to never-users in 5 studies that were the largest homogeneous group of studies. Range of estimates is best-case and worst-case scenarios rather than CIs <sup>g</sup>
<b>HIV studies cited in NIH report (1)</b>				
Davis & Weller 1999 (2)	As Weller & Davis (3) above	25 studies of serodiscordant couples, including 13 cross-sectional studies and 12 longitudinal studies	As Weller & Davis above	Point estimate is the IRR <sup>h</sup> of always-users in 12 longitudinal studies to never-users in 7 longitudinal studies that specified direction of transmission. Range of estimates is best-case and worst-case scenarios rather than CIs
Pinkerton and Abramson (11)	As Weller & Davis (3) above	9 studies of serodiscordant couples	Consistent condom use versus inconsistent use or no use	Point estimate is RR for always-users to inconsistent-users or non-users for all 9 studies
<b>HSV-2<sup>b</sup> studies</b>				
Wald et al. 2001 (12)	Randomized, double-blind, placebo-controlled trial of candidate HSV-2 vaccine in USA with 11 follow-up visits over 18 months	528 monogamous couples serodiscordant for HSV-2, including 267 couples with seronegative women and 261 couples with seronegative men	Condom use in more than 25% of sexual acts between follow-up visits	Estimates adjust for covariates
Wald et al., unpublished data, 2002	Candidate HSV-2 vaccine trial in USA with 18 months of follow-up	1862 HSV-2 susceptible people with ≥ 4 sexual partners or ≥ 1 STD in the past year	Condom use in more than 65% of sexual acts	Complete data not yet published
<b>Bacterial and parasitic STIs</b>				
Sanchez et al. 2003 (13)	Prospective study of condom promotion and improved STI services at two clinics in Lima, Peru, with monthly follow-up for 6 months	917 female sex workers who attended the clinics	Participants who always used condoms with clients during the previous month versus all others	GEE <sup>i</sup> model. Covariates differ across infections. Published OR <sup>j</sup> and P-values were used to derive 95% CI. For gonorrhoea, the P-value (<0.001) was not exact, so the actual CI is shorter than the one reported in Fig. 1
Macaluso et al., unpublished data, 2000	Prospective study of a behavioural intervention to promote use of the female condom in USA with follow-up every 4 weeks for 6 months	920 females who attended public STI clinics	Consistent use of male condoms or female condoms between follow-up visits with no problems reported versus condom use in ≤ 50 % of sex acts	Outcome was incidence of gonorrhoea, chlamydial infection, or syphilis. Complete data not yet published

(Table 1, cont.)

Study	Design	Participants	Definition of condom use	Notes on estimates
Crosby et al. 2003 (14)	Randomized controlled trial of an HIV prevention programme in USA with follow-up visit after 6 months	380 sexually active African-American females aged 14–18 years recruited from medical clinics and high schools	Consistent condom use versus non-consistent use	Outcome was incidence of gonorrhoea, chlamydial infection, or trichomoniasis. Estimates adjusted for covariates. The OR presented in Fig. 1 is the inverse of the results reported in Crosby et al. (14)
Ahmed et al. 2001 (10)	See entry under HIV above	See entry under HIV above	See entry under HIV above	GEE model adjusted for covariates
<b>Bacterial and parasitic STIs cited in NIH report (1)</b>				
Hooper et al. 1978 (4)	Prospective cohort study to estimate the risk of transmission of gonorrhoea from infected females to males at a port in the western Pacific	527 male American sailors who had sexual relations with commercial sex workers during a four-day shore leave	Condom use sometimes or always versus non-use	Published data and P-value were used to derive a CI for the OR based on an exact procedure
Cates & Holmes 1996 (5)	Reanalysis of Hooper et al.'s 1978 data that estimated the risk of acquisition of gonorrhoea or nongonococcal urethritis	As in Hooper et al. (4) above	As in Hooper et al. above	Published data and P-value were used to derive a CI for the OR based on an exact procedure
Bunnell et al. 1999 (15)	Prospective cohort study to assess the prevalence and incidence of STIs among adolescents in USA with one follow-up visit after 6 months	484 sexually active African-American females aged 14–19 years recruited from four health clinics	Consistent condom use reported at both baseline and follow-up (i.e. always used condom for birth control and with main partner) versus all others	Outcome was incident STIs, including gonorrhoea, chlamydial infection, trichomoniasis, syphilis, hepatitis B, and HSV-2. Estimates adjusted for covariates
Zenilman et al. 1995 (16)	Prospective cohort study to validate self-reported condom use in USA with one follow-up visit after 3 months	275 female patients and 323 male patients at two public STI clinics	Consistent condom use in 30 days before follow-up visit versus never use	Outcome was incident gonorrhoea, chlamydial infection, syphilis, or trichomoniasis. Estimates adjusted for covariates
<b>HPV<sup>c</sup> studies</b>				
Manhart & Koutsky 2002 (22)	Meta-analysis of condom effectiveness in preventing HPV or HPV-related conditions (genital warts, CIN <sup>d</sup> , ICC <sup>e</sup> ) in studies in several countries	20 studies, of which only two were prospective: Ho et al. 1998 (17) and Zondervan et al. 1996 (18). These are included in Fig. 1	Ho: Consistent use versus never use	Ho: Outcome was cervical HPV DNA. Investigators provided additional data for meta-analysis. Estimates adjusted for covariates
Winer et al. 2003 (19)	Prospective study to estimate cumulative incidence of HPV in USA with follow-up every 4 months for 3 years	444 female university students aged 18–20 years who tested negative for HPV DNA at baseline	Zondervan: Ever use condoms for family planning versus never use Condom use always with new partners versus never use with new partners	Zondervan: Outcomes were dysplasia (which probably refers to mild SIL), carcinoma in situ (which refers to CIN) and ICC. Estimates adjusted for covariates Estimates adjusted for covariates

(Table 1, cont.)

Study	Design	Participants	Definition of condom use	Notes on estimates
Hogewoning et al. 2003 (20)	Randomized clinical trial of condom effectiveness in the Netherlands with follow-up at 3, 6, 12, 18 and 24 months	135 women with CIN who were not using condoms for birth control at baseline were randomly allocated. Outcomes were assessed for 125 women	Assigned to use condoms or not to use them	Outcomes were clinical regression of CIN and clearance of HPV. Estimates adjusted for covariates. Published HR <sup>k</sup> of the probability of healing was inverted to show the effect of condoms in reducing the probability of not healing
Bleeker et al. 2003 (21)	As Hogewoning et al. (20) above	100 men who were partners of the women in Hogewoning et al. and who had penile lesions were assessed for outcomes	As Hogewoning et al. above	Estimates adjusted for covariates. Published HR of the probability of regression was inverted to show the effect of condoms in reducing the probability of not regressing

<sup>a</sup> HIV = human immunodeficiency virus; STIs = sexually transmitted infections.

<sup>b</sup> HSV-2 = herpes simplex virus type 2.

<sup>c</sup> HPV = human papillomavirus.

<sup>d</sup> CIN = cervical intraepithelial neoplasia.

<sup>e</sup> ICC = invasive cervical cancer.

<sup>f</sup> IRR = incidence rate ratio.

<sup>g</sup> CI = confidence interval.

<sup>h</sup> RR = relative risk.

<sup>i</sup> GEE = generalized estimating equation.

<sup>j</sup> OR = odds ratio.

<sup>k</sup> HR = hazard ratio.

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## Sexually Transmitted Infections Treatment Guidelines, 2021



U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

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# Sexually Transmitted Infections Treatment Guidelines, 2021

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## Summary

These guidelines for the treatment of persons who have or are at risk for sexually transmitted infections (STIs) were updated by CDC after consultation with professionals knowledgeable in the field of STIs who met in Atlanta, Georgia, June 11–14, 2019. The information in this report updates the 2015 guidelines. These guidelines discuss 1) updated recommendations for treatment of Neisseria gonorrhoeae, Chlamydia trachomatis, and Trichomonas vaginalis; 2) addition of metronidazole to the recommended treatment regimen for pelvic inflammatory disease; 3) alternative treatment options for bacterial vaginosis; 4) management of Mycoplasma genitalium; 5) human papillomavirus vaccine recommendations and counseling messages; 6) expanded risk factors for syphilis testing among pregnant women; 7) one-time testing for hepatitis C infection; 8) evaluation of men who have sex with men after sexual assault; and 9) two-step testing for serologic diagnosis of genital herpes simplex virus. Physicians and other health care providers can use these guidelines to assist in prevention and treatment of STIs.

## Introduction

The term “sexually transmitted infection” (STI) refers to a pathogen that causes infection through sexual contact, whereas the term “sexually transmitted disease” (STD) refers to a recognizable disease state that has developed from an infection. Physicians and other health care providers have a crucial role in preventing and treating STIs. These guidelines are intended to assist with that effort. Although the guidelines emphasize treatment, prevention strategies and diagnostic recommendations also are discussed.

This report updates *Sexually Transmitted Diseases Treatment Guidelines, 2015* (1) and should be regarded as a source of clinical guidance rather than prescriptive standards. Health care providers should always consider the clinical circumstances of each person in the context of local disease prevalence. These guidelines are applicable to any patient care setting that serves persons at risk for STIs, including family planning clinics, HIV care clinics, correctional health care settings, private physicians' offices, Federally Qualified Health Centers, clinics for adolescent care, and other primary care facilities. These guidelines are focused on treatment and counseling and do not address other community services and interventions that are essential to STI and HIV prevention efforts.

These STI treatment guidelines complement *Recommendations for Providing Quality Sexually Transmitted Diseases Clinical Services, 2020* (2) regarding quality clinical services for STIs in primary care and STD specialty care settings. This guidance specifies operational determinants of quality services in various clinical settings, describes on-site treatment and partner services, and indicates when STI-related conditions should be managed through consultation with or referral to a specialist.

## Methods

These guidelines were developed by CDC staff who worked with subject matter experts with expertise in STI clinical management from other federal agencies, nongovernmental academic and research institutions, and professional medical organizations. CDC staff identified governmental and nongovernmental subject matter experts on the basis of their expertise and assisted them in developing questions to guide individual literature reviews. CDC staff informed the subject matter experts that they were being consulted to exchange information and observations and to obtain their individual input. All subject matter experts disclosed potential conflicts of interest. STI Treatment Guidelines, 2021, Work Group members are listed at the end of this report.

In 2018, CDC staff identified key questions about treatment and clinical management to guide an update of the 2015 STD treatment guidelines (1). To answer these questions and synthesize new information available since publication of the 2015 guidelines, subject matter experts and CDC staff

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collaborated to conduct systematic literature reviews by using an extensive MEDLINE database evidence-based approach for each section of the 2015 guidelines (e.g., using English-language published abstracts and peer reviewed journal articles). These systematic reviews were focused on four principal outcomes of STI therapy for each disease or infection: 1) treatment of infection on the basis of microbiologic eradication; 2) alleviation of signs and symptoms; 3) prevention of sequelae; and 4) prevention of transmission, including advantages (e.g., cost-effectiveness, single-dose formulations, and directly observed therapy) and disadvantages (e.g., adverse effects) of specific regimens. The outcome of the literature reviews guided development of background materials, including tables of evidence from peer-reviewed publications summarizing the type of study (e.g., randomized controlled trial or case series), study population and setting, treatments or other interventions, outcome measures assessed, reported findings, and weaknesses and biases in study design and analysis.

In June 2019, the subject matter experts presented their assessments of the literature reviews at an in-person meeting of governmental and nongovernmental participants. Each key question was discussed and pertinent publications were reviewed in terms of strengths, weaknesses, and relevance. Participants evaluated the quality of evidence, provided their input, and discussed findings in the context of the modified rating system used by the U.S. Preventive Services Task Force (USPSTF). The discussions were informal and not structured to reach consensus. CDC staff also reviewed the publications from other professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), USPSTF, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the Advisory Committee on Immunization Practices (ACIP). The discussion culminated in a list of participants' opinions on all the key STI topic areas for consideration by CDC. (More detailed descriptions of the key questions, search terms, systematic search, evidence tables, and review process are available at <https://www.cdc.gov/std/treatment-guidelines/default.htm>).

CDC staff then independently reviewed the tables of evidence prepared by the subject matter experts, individual comments from the participants and professional organizations, and existing guidelines from other organizations to determine whether revisions to the 2015 STD treatment guidelines were warranted. CDC staff ranked evidence as high, medium, and low on the basis of each study's strengths and weaknesses according to the USPSTF ratings (<https://www.uspreventiveservicestaskforce.org/uspstf/us-preventive-services-task-force-ratings>). CDC staff then developed draft recommendations that were peer reviewed by public health and clinical experts as defined by the Office of

Management and Budget for influential scientific information. A public webinar was held to provide an overview of the draft recommendations and invite questions and comments on the draft recommendations. The peer review comments, webinar, questions, and responses were considered by CDC staff in developing the final recommendations for the updated STI treatment guidelines. Recommendations for HIV, hepatitis C, cervical cancer screening, STI screening in pregnancy, human papillomavirus (HPV) testing, and hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccination were developed after CDC staff reviewed existing published recommendations. The English-language literature was searched periodically by CDC staff to identify subsequently published articles warranting consideration.

Throughout this report, the evidence used as the basis for specific recommendations is discussed briefly. Publication of comprehensive, annotated discussions of such evidence is planned in a supplemental issue of the journal *Clinical Infectious Diseases* after publication of the treatment guidelines. When more than one therapeutic regimen is recommended and the listed regimens have similar efficacy and similar rates of intolerance or toxicity, the recommendations are listed alphabetically. If differences are specified, regimens are prioritized on the basis of these differences. Recommended regimens should be used primarily; alternative regimens can be considered in instances of notable drug allergy or other medical contraindications to the recommended regimens. Alternative regimens are considered inferior to recommended regimens on the basis of available evidence regarding the principal outcomes and disadvantages of the regimens.

## Clinical Prevention Guidance

Prevention and control of STIs are based on the following five major strategies (3):

1. Accurate risk assessment and education and counseling of persons at risk regarding ways to avoid STIs through changes in sexual behaviors and use of recommended prevention services
2. Pre-exposure vaccination for vaccine-preventable STIs
3. Identification of persons with an asymptomatic infection and persons with symptoms associated with an STI
4. Effective diagnosis, treatment, counseling, and follow-up of persons who are infected with an STI
5. Evaluation, treatment, and counseling of sex partners of persons who are infected with an STI

## STI and HIV Infection Risk Assessment

Primary prevention of STIs includes assessment of behavioral risk (i.e., assessing the sexual behaviors that can place persons at risk for infection) and biologic risk (i.e., testing for risk markers for STI and HIV acquisition or transmission). As part of the clinical encounter, health care providers should routinely obtain sexual histories from their patients and address risk reduction as indicated in this report. Guidance for obtaining a sexual history is available at the Division of STD Prevention resource page (<https://www.cdc.gov/std/treatment/resources.htm>) and in the curriculum provided by the National Network of STD Clinical Prevention Training Centers (<https://www.nnptc.org>). Effective interviewing and counseling skills, characterized by respect, compassion, and a nonjudgmental attitude toward all patients, are essential to obtaining a thorough sexual history and delivering effective prevention messages. Effective techniques for facilitating rapport with patients include using open-ended questions (e.g., “Tell me about any new sex partners you’ve had since your last visit” and “What has your experience with using condoms been like?”); understandable, nonjudgmental language (e.g., “What gender are your sex partners?” and “Have you ever had a sore or scab on your penis?”); and normalizing language (e.g., “Some of my patients have difficulty using a condom with every sex act. How

is it for you?”). The “Five P’s” approach to obtaining a sexual history is one strategy for eliciting information about the key areas of interest (Box 1). In addition, health care professionals can consider assessing sexual history by asking patients such questions as, “Do you have any questions or concerns about your sexual health?” Additional information about gaining cultural competency when working with certain populations (e.g., gay, bisexual, or other men who have sex with men [MSM]; women who have sex with women [WSW] or with women and men [WSWM]; or transgender men and women or adolescents) is available in sections of these guidelines related to these populations.

In addition to obtaining a behavioral risk assessment, a comprehensive STI and HIV risk assessment should include STI screening as recommended in these guidelines because STIs are biologic markers of risk, particularly for HIV acquisition and transmission among certain MSM. In most clinical settings, STI screening is an essential and underused component of an STI and HIV risk assessment. Persons seeking treatment or evaluation for a particular STI should be screened for HIV and other STIs as indicated by community prevalence and individual risk factors (see Chlamydial Infections; Gonococcal Infections; Syphilis). Persons should be informed about all the tests for STIs they are receiving and notified about tests for common STIs (e.g., genital herpes,

### BOX 1. The Five P's approach for health care providers obtaining sexual histories: partners, practices, protection from sexually transmitted infections, past history of sexually transmitted infections, and pregnancy intention

#### 1. Partners

- “Are you currently having sex of any kind?”
- “What is the gender(s) of your partner(s)?”

#### 2. Practices

- “To understand any risks for sexually transmitted infections (STIs), I need to ask more specific questions about the kind of sex you have had recently.”
- “What kind of sexual contact do you have or have you had?”
  - “Do you have vaginal sex, meaning ‘penis in vagina’ sex?”
  - “Do you have anal sex, meaning ‘penis in rectum/anus’ sex?”
  - “Do you have oral sex, meaning ‘mouth on penis/vagina?’”

#### 3. Protection from STIs

- “Do you and your partner(s) discuss prevention of STIs and human immunodeficiency virus (HIV)?”
- “Do you and your partner(s) discuss getting tested?”
- For condoms:
  - “What protection methods do you use? In what situations do you use condoms?”

#### 4. Past history of STIs

- “Have you ever been tested for STIs and HIV?”
- “Have you ever been diagnosed with an STI in the past?”
- “Have any of your partners had an STI?”

#### Additional questions for identifying HIV and viral hepatitis risk:

- “Have you or any of your partner(s) ever injected drugs?”
- “Is there anything about your sexual health that you have questions about?”

#### 5. Pregnancy intention

- “Do you think you would like to have (more) children in the future?”
- “How important is it to you to prevent pregnancy (until then)?”
- “Are you or your partner using contraception or practicing any form of birth control?”
- “Would you like to talk about ways to prevent pregnancy?”

trichomoniasis, *Mycoplasma genitalium*, and HPV) that are available but not being performed and reasons why they are not always indicated. Persons should be informed of their test results and recommendations for future testing. Efforts should be made to ensure that all persons receive STI care regardless of personal circumstances (e.g., ability to pay, citizenship or immigration status, gender identity, language spoken, or specific sex practices).

## STI and HIV Infection Prevention Counseling

After obtaining a sexual history from their patients, all providers should encourage risk reduction by offering prevention counseling. Prevention counseling is most effective if provided in a nonjudgmental and empathetic manner appropriate to the patient's culture, language, sex and gender identity, sexual orientation, age, and developmental level. Prevention counseling for STIs and HIV should be offered to all sexually active adolescents and to all adults who have received an STI diagnosis, have had an STI during the previous year, or have had multiple sex partners. USPSTF recommends intensive behavioral counseling for all sexually active adolescents and for adults at increased risk for STIs and HIV (4). Such interactive counseling, which can be resource intensive, is directed at a person's risk, the situations in which risk occurs, and the use of personalized goal-setting strategies. One such approach, known as client-centered STI and HIV prevention counseling, involves tailoring a discussion of risk reduction to the person's situation. Although one large study in STI clinics (Project RESPECT) demonstrated that this approach was associated with lower acquisition of curable STIs (e.g., trichomoniasis, chlamydia, gonorrhea, and syphilis) (5), another study conducted 10 years later in the same settings but different contexts (Project AWARE) did not replicate this result (6).

With the challenges that intensive behavioral counseling poses, health care professionals might find brief prevention messages and those delivered through video or in a group session to be more accessible for the client. A review of 11 studies evaluated brief prevention messages delivered by providers and health counselors and reported them to be feasible and to decrease subsequent STIs in STD clinic settings (7) and HIV care settings (8). Other approaches use motivational interviewing to move clients toward achievable risk-reduction goals. Client-centered counseling and motivational interviewing can be used effectively by clinicians and staff trained in these approaches. CDC provides additional information on these and other effective behavioral interventions at <https://www.cdc.gov/std/program/interventions.htm>. Training in client-centered counseling and motivational interviewing is available through

the STD National Network of Prevention Training Centers (<https://www.nnptc.org>).

In addition to one-on-one STI and HIV prevention counseling, videos and large group presentations can provide explicit information concerning STIs and reducing disease transmission (e.g., how to use condoms consistently and correctly and the importance of routine screening). Group-based strategies have been effective in reducing the occurrence of STIs among persons at risk, including those attending STD clinics (9). Brief, online, electronic-learning modules for young MSM have been reported to be effective in reducing incident STIs and offer a convenient client platform for effective interventions (10). Because the incidence of certain STIs, most notably syphilis, is higher among persons with HIV infection, use of client-centered STI counseling for persons with HIV continues to be encouraged by public health agencies and other health organizations (<https://www.cdc.gov/std/statistics/2019/default.htm>). A 2014 guideline from CDC, the Health Resources and Services Administration, and the National Institutes of Health recommends that clinical and nonclinical providers assess a person's behavioral and biologic risks for acquiring or transmitting STIs and HIV, including having sex without condoms, having recent STIs, and having partners recently treated for STIs (<https://stacks.cdc.gov/view/cdc/44064>). That federal guideline is for clinical and nonclinical providers to offer or make referral for regular screening for multiple STIs, on-site STI treatment when indicated, and risk-reduction interventions tailored to the person's risks. Brief risk-reduction counseling delivered by medical providers during HIV primary care visits, coupled with routine STI screening, has been reported to reduce STI incidence among persons with HIV infection (8). Other specific methods have been designed for the HIV care setting (<https://www.cdc.gov/hiv/effective-interventions/index.html>).

## Primary Prevention Methods

### Pre-Exposure Vaccination

Pre-exposure vaccination is one of the most effective methods for preventing transmission of HPV, HAV, and HBV, all of which can be sexually transmitted. HPV vaccination is recommended routinely for males and females aged 11 or 12 years and can be administered beginning at age 9 years. HPV vaccination is recommended through age 26 years for those not previously vaccinated (11). Sharing clinical decision-making about HPV vaccination is recommended for certain adults aged 27–45 years who are not adequately vaccinated in accordance with existing guidance (<https://www.cdc.gov/vaccines/hcp/acip-recommendations/vaccine-specific/hpv.html>).

Hepatitis B vaccination is recommended for all unvaccinated, uninfected persons who are sexually active with more than one partner or are being evaluated or treated for an STI (12). In addition, hepatitis A and B vaccines are recommended for MSM, persons who inject drugs, persons with chronic liver disease, and persons with HIV or hepatitis C infections who have not had hepatitis A or hepatitis B (12). HAV vaccine is also recommended for persons who are homeless (13). Details regarding HAV and HBV vaccination, including routine childhood vaccination, are available at <https://www.cdc.gov/hepatitis> and at the ACIP website (<https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html>).

## Condoms

### External Condoms

When used consistently and correctly, external latex condoms, also known as male condoms, are effective in preventing the sexual transmission of HIV infection ([http://www.ashasexualhealth.org/pdfs/Male\\_and\\_Female\\_Condoms.pdf](http://www.ashasexualhealth.org/pdfs/Male_and_Female_Condoms.pdf)). In heterosexual HIV mixed-status relationships (i.e., those involving one infected and one uninfected partner) in which condoms were used consistently, HIV-negative partners were 71%–80% less likely to become infected with HIV, compared with persons in similar relationships in which condoms were not used (14,15). Two analyses of MSM mixed-status couple studies estimated the protective effect of condom use to be 70% and 91%, respectively (16,17). Moreover, studies demonstrate that consistent condom use reduces the risk for other STIs, including chlamydia, gonorrhea, hepatitis B, and trichomoniasis (18–21). By limiting lower genital tract infections, condoms also might reduce the risk for pelvic inflammatory disease (PID) among women (22). In addition, consistent and correct use of latex condoms reduces the risk for HPV infection and HPV-associated diseases, genital herpes, syphilis, and chancroid when the infected area or site of potential exposure is covered (23–27). Additional information is available at <https://www.cdc.gov/condomeffectiveness/index.html> and [www.factsaboutcondoms.com/professional.php](http://www.factsaboutcondoms.com/professional.php). Condoms are regulated as medical devices and are subject to random sampling and testing by the Food and Drug Administration (FDA). Each latex condom manufactured in the United States is tested electronically for holes before packaging. The rate of condom breakage during sexual intercourse and withdrawal in the United States is approximately two broken condoms per 100 condoms. Rates of breakage and slippage might be slightly higher during anal intercourse (28,29). The failure of condoms to protect against STIs or unintended pregnancy usually results from inconsistent or incorrect use rather than condom breakage (30). Users should check the expiration or manufacture date

on the box or individual package. Latex condoms should not be used beyond their expiration date or >5 years after the manufacturing date. Condoms made of materials other than latex are available in the United States and can be classified into two general categories: 1) polyurethane, polyisoprene, or other synthetic condoms and 2) natural membrane condoms.

Polyurethane external condoms provide protection against STIs and HIV and pregnancy comparable to that of latex condoms (20,31). These can be substituted for latex condoms by persons with latex sensitivity, are typically more resistant to deterioration, and are compatible with use of both oil-based and water-based lubricants. The effectiveness of other synthetic external condoms to prevent STIs has not been extensively studied, and FDA labeling restricts their recommended use to persons who are sensitive to or allergic to latex. Natural membrane condoms (frequently called natural skin condoms or [incorrectly] lambskin condoms) are made from lamb cecum and can have pores up to 1,500 nm in diameter. Although these pores do not allow the passage of sperm, they are more than 10 times the diameter of HIV and more than 25 times that of HBV. Moreover, laboratory studies demonstrate that sexual transmission of viruses, including HBV, herpes simplex virus (HSV), and HIV, can occur with natural membrane condoms (31). Therefore, natural membrane condoms are not recommended for prevention of STIs and HIV.

Providers should advise that condoms must be used consistently and correctly to be effective in preventing STIs and HIV while noting that any condom use is better than no condom use. Providing instructions about the correct use of condoms can be useful. Communicating the following recommendations can help ensure that patients use external condoms correctly:

- Use a new condom with each sex act (i.e., oral, vaginal, and anal).
- Carefully handle the condom to avoid damaging it with fingernails, teeth, or other sharp objects.
- Put the condom on after the penis is erect and before any genital, oral, or anal contact with the partner.
- Use only water-based or silicone-based lubricants (e.g., K-Y Jelly, Astroglide, AquaLube, or glycerin) with latex condoms. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, or cooking oil) can weaken latex and should not be used; however, oil-based lubricants typically can be used with polyurethane or other synthetic condoms.
- Ensure adequate lubrication during vaginal and anal sex, which might require using exogenous water-based lubricants.
- Hold the condom firmly against the base of the penis during withdrawal, and withdraw while the penis is still erect to prevent the condom from slipping off.

Additional information about external condoms is available at <https://www.cdc.gov/condomeffectiveness>.

### **Internal Condoms**

Condoms for internal vaginal use, also known as female condoms, are available worldwide (e.g., the FC2 Female Condom, Reddy condom, Cupid female condom, and Woman's condom) (31,32). Use of internal condoms can provide protection from acquisition and transmission of STIs, although data are limited. Internal condoms are more costly compared with external condoms; however, they offer the advantage of being controlled by the receptive partner as an STI and HIV prevention method, and the newer versions might be acceptable to all persons. Although the internal condom also has been used during receptive anal intercourse, efficacy associated with this practice remains unknown (33). Additional information about the internal condom is available at [http://www.ashasexualhealth.org/pdfs/Male\\_and\\_Female\\_Condoms.pdf](http://www.ashasexualhealth.org/pdfs/Male_and_Female_Condoms.pdf).

### **Cervical Diaphragms**

In observational studies, diaphragm use has been demonstrated to protect against cervical gonorrhea, chlamydia, and trichomoniasis (34). However, a trial examining the effect of a diaphragm plus lubricant on HIV acquisition among women in Africa reported no additional protective effect when compared with the use of male condoms alone. Likewise, no difference by study arm in the rate of acquisition of chlamydia, gonorrhea, or herpes occurred (35,36). Diaphragms should not be relied on as the sole source of protection against HIV and other STIs.

### **Multipurpose Prevention Technologies**

Methods that combine STI and HIV prevention with pregnancy prevention are known as multipurpose prevention technologies (MPTs) (37) (<https://www.who.int/reproductivehealth/topics/linkages/mpts/en>). Internal and external condoms are both examples of MPTs because they are effective prevention measures when used correctly for STI and HIV transmission or pregnancy prevention. The multicenter Evidence for Contraception Options and HIV Outcomes (ECHO) trial observed no statistically significant differences in HIV incidence rates among women randomly assigned to one of three contraceptive methods (depot medroxyprogesterone acetate [DMPA], levonorgestrel implant, and copper-containing intrauterine device [IUD]); however, rates of HIV infection were high in all groups, indicating a need for MPTs (38). Development of MPTs is complex and ongoing; products under study include microbicides with contraceptive devices (e.g., tenofovir with a vaginal ring contraceptive delivery package) and other innovative methods (39).

### **Topical Microbicides and Spermicides**

Nonspecific topical microbicides are ineffective for preventing HIV infection (40–45). Tenofovir gel has been studied for prevention of herpes simplex virus 2 (HSV-2) and HIV infections (46,47). Adherence can be low (48), and prevention of HIV infection, especially among women, has not been demonstrated (47,49). Vaginal rings containing dapivirine have provided some reduction in HIV infection (50,51). For men and transgender women who have anal intercourse, tenofovir gel appears safe when applied before and after anal sex (52). Spermicides containing nonoxynol-9 (N-9) might disrupt genital or rectal epithelium and have been associated with an increased risk for HIV infection. Condoms with N-9 are no more effective than condoms without N-9; therefore, N-9 alone or in a condom is not recommended for STI and HIV prevention (40). N-9 use also has been associated with an increased risk for bacterial urinary tract infections among women (53,54).

### **Nonbarrier Contraception, Female Surgical Sterilization, and Hysterectomy**

Contraceptive methods that are not mechanical barriers offer no protection against HIV or other STIs. The ECHO study observed no differences in HIV incidence rates among women randomly assigned to DMPA, levonorgestrel implant, or copper-containing IUD contraceptive methods (38). A systematic review of epidemiologic evidence reported that the majority of studies demonstrated no association between use of oral contraceptives and HIV acquisition among women (55). Whether hormonal contraception alters a woman's risk for other STIs is uncertain (56,57).

Sexually active women who use contraceptive methods other than condoms should be counseled about STI and HIV infection prevention measures. These include pre-exposure prophylaxis (PrEP) and postexposure prophylaxis (PEP), limiting the number of sex partners, and correct and consistent use of condoms.

### **Emergency Contraception**

Unprotected intercourse exposes women to risks for STIs and unplanned pregnancy. Providers should offer counseling about the option of emergency contraception if pregnancy is not desired. Options for emergency contraception in the United States include copper-containing IUDs and emergency contraceptive pills (ECPs) (58,59). More information is available at [https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2015/09/emergency-contraception?utm\\_source=redirect&utm\\_medium=web&utm\\_campaign=otn](https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2015/09/emergency-contraception?utm_source=redirect&utm_medium=web&utm_campaign=otn). ECPs are available in the following formulations: ulipristal

acetate in a single dose (30 mg) available by prescription, levonorgestrel in a single dose (1.5 mg) available over the counter or by prescription, or a combined estrogen and progestin pill regimen. Insertion of a copper-containing IUD ≤5 days after unprotected sex can reduce pregnancy risk from a sex act by approximately 99% (60). ECPs are most efficacious when initiated as soon as possible after unprotected sex. Ulipristal acetate is effective ≤5 days after unprotected sex, and levonorgestrel is most effective ≤3 days after unprotected sex but has some efficacy at ≤5 days. ECPs are ineffective (but not harmful) if the woman is already pregnant (61). A 2019 Cochrane review summarized the efficacy, safety, and convenience of different emergency contraception methods (61).

More information about emergency contraception is available in *Contraceptive Technology, 21st Edition* (31), in the 2016 U.S. Selected Practice Recommendations (U.S. SPR) for Contraceptive Use (emergency contraception) available at <https://www.cdc.gov/reproductivehealth/contraception/mmwr/spr/emergency.html>, and in the 2016 U.S. Medical Eligibility Criteria (U.S. MEC) for Contraceptive Use (copper IUDs for emergency contraception) available at <https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/appendixj.html>.

Providers should educate males and females about emergency contraception, especially if other methods of contraception were used incorrectly or not at all and pregnancy is not desired (62). An advance supply of ECPs can be provided or prescribed so that ECPs will be available when needed (59).

## Male Circumcision

Male circumcision reduces the risk for HIV infection and certain STIs among heterosexual men. Three randomized, controlled trials performed in regions of sub-Saharan Africa, where generalized HIV epidemics involving predominantly heterosexual transmission were occurring, demonstrated that male circumcision reduces the risk for HIV acquisition among men by 50%–60% (63–65). In those trials, circumcision also was protective against other STIs, including high-risk genital HPV infection and genital herpes (66–68). Follow-up studies have demonstrated sustained benefit of circumcision for HIV prevention (69) and that the effect is not mediated solely through a reduction in HSV-2 infection or genital ulcer disease (GUD) (70).

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend that male circumcision efforts be scaled up as an effective intervention for preventing heterosexually acquired HIV infection (71) in countries with hyperendemic and generalized HIV epidemics within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support

(<https://www.afro.who.int/publications/voluntary-medical-male-circumcision-hiv-prevention>). In the United States, the American Academy of Pediatrics (AAP) recommends that newborn male circumcision be available to families that desire it because the benefits of the procedure, including prevention of penile cancers, urinary tract infections, GUD, and HIV infection, outweigh the risks. ACOG has also endorsed AAP's policy statement. In light of these benefits, the American Urological Association states that male circumcision should be considered an option for risk reduction, among other strategies (72). Additional information for providers counseling male patients and parents regarding male circumcision for preventing HIV, STIs, and other adverse health outcomes is available at <https://www.cdc.gov/hiv/risk/male-circumcision.html>.

No definitive data exist to determine whether male circumcision reduces HIV acquisition among MSM, although one meta-analysis of 62 observational studies reported that circumcision was protective against HIV acquisition in low- to middle-income countries but not in high-income countries (73). Further studies are needed to confirm any potential benefit of male circumcision for this population.

## Pre-Exposure Prophylaxis for HIV

Daily oral antiretroviral PrEP with a fixed-dose combination of emtricitabine (FTC) and either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) have demonstrated safety (74) and a substantial reduction in the rate of HIV acquisition for MSM (75). TDF/FTC has demonstrated safety and efficacy for mixed-status heterosexual couples (76) and heterosexual men and women recruited individually (77); however, no evidence is yet available regarding TAF/FTC among heterosexually active women. In addition, one clinical trial involving persons who inject drugs (78) and one involving heterosexual mixed-status couples (76) demonstrated substantial efficacy and safety of daily oral PrEP with TDF alone. High adherence to oral PrEP was strongly associated with protection from HIV infection. Studies conducted with MSM have demonstrated that taking PrEP at specific times before and after sexual intercourse was effective in preventing HIV; however, less experience exists with this regimen, it is not FDA cleared, and it has not been studied among other populations (79).

Comprehensive clinical practice guidelines are available for providers in prescribing PrEP to reduce the risk for HIV infection (80). Among HIV-negative sexually active men and women, bacterial STIs are key indicators of risk for HIV acquisition. Studies have documented the risk for HIV acquisition among MSM within 1 year after infection with rectal gonorrhea or chlamydia (one in 15 men), primary or secondary syphilis (one in 18), and among men with no

rectal STI or syphilis infection (one in 53) (81–83). Sexually active adults and adolescents should be screened for STIs (e.g., chlamydia, gonorrhea, and syphilis) in accordance with recommendations, and persons with infection should be offered PrEP. The USPSTF recommends that persons at risk for HIV acquisition be offered PrEP (84). Persons at risk for HIV acquisition include HIV-negative persons whose sexual partner or partners have HIV infection (especially if viral load is detectable or unknown), persons who have had gonorrhea or syphilis during the previous 6 months, and injecting drug users who share injection equipment (84). Clinical practice guidelines recommend STI screening for persons taking PrEP (80) because increased rates of STI acquisition have been described (85–87).

### **Pre-Exposure Prophylaxis for STIs**

Providing HSV treatment to persons with HIV and HSV infection has not demonstrated benefit in reducing HIV acquisition among uninfected partners. A large randomized controlled trial evaluated mixed-status heterosexual couples among the partners with HIV infection who also were seropositive for HSV-2 (88). Use of acyclovir had no effect on HIV transmission. These findings are consistent with a previous trial that reported no benefit of acyclovir in preventing HIV acquisition among persons seropositive for HSV-2 (89).

Doxycycline prophylaxis has been examined for preventing bacterial STIs. In a pilot study, 30 MSM living with HIV with previous syphilis (two or more episodes since HIV diagnosis) were randomly assigned to doxycycline 100 mg for 48 weeks versus a financial incentive–based behavioral intervention (90). That study demonstrated a 73% reduction in any bacterial STI at any site, without substantial differences in sexual behavior. Additional studies examining doxycycline prophylaxis are under way or in development (91).

### **Postexposure Prophylaxis for HIV and STIs**

Guidelines for using PEP aimed at preventing HIV and other STIs as a result of sexual exposure are available at <https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf>. Sexually active persons seeking HIV PEP should be evaluated for PrEP after completing their PEP course and testing negative for HIV. HIV PEP is also discussed elsewhere in this report (see Sexual Assault and Abuse and STIs). Genital hygiene methods (e.g., vaginal washing and douching) after sexual exposure are ineffective in protecting against HIV and STIs and might increase the risk for bacterial vaginosis (BV), certain STIs, and HIV infection (92).

STI PEP in the form of doxycycline 200 mg taken after unprotected anal sex has been studied among MSM and transgender women; results demonstrated reduction in incident

chlamydia and syphilis by 70% and 73%, respectively, but no effect on gonorrhea (93). Other studies are under way or in development regarding doxycycline prophylaxis for bacterial STIs (91). No long-term data are available regarding the impact of STI PEP on antimicrobial resistance and the microbiome. Further studies are needed to determine whether STI PEP is an effective and beneficial strategy for STI prevention.

### **HIV Treatment as Prevention: Antiretroviral Treatment of Persons with HIV to Prevent HIV Among Partners**

In 2011, the randomized controlled trial HPTN 052 demonstrated that, among HIV mixed-status heterosexual couples, HIV antiretroviral therapy (ART) for the infected partner decreased the risk for transmission to the uninfected partner by 96% (94). Therefore, ART not only is beneficial to the health of persons with HIV infection, it also reduces the risk for transmission. Additional studies of HIV mixed-status couples, heterosexual and MSM couples (PARTNER study), and MSM couples (Opposites Attract and PARTNERS2 studies) reported that patients with HIV taking ART who maintain an undetectable viral load demonstrate no risk for transmitting HIV to their HIV-negative sex partners (95–97). For those reasons, ART should be offered to all persons with HIV infection to obtain viral suppression. Detailed guidance regarding ART regimens is available in the U.S. Department of Health and Human Services' HIV treatment guidelines (98).

### **HIV Seroadaptive Strategies**

Seroadaptive strategies for HIV prevention have largely originated within communities of MSM. They are predicated on knowledge of self and partner HIV status. One specific seroadaptive practice is serosorting, which includes limiting anal sex without a condom to partners with the same HIV status as their own or choosing to selectively use condoms with HIV mixed-status partners. Another practice among mixed-status couples is seropositioning, in which the person with HIV infection is the receptive partner for anal intercourse. Observational studies have consistently reported that serosorting confers greater risk for HIV infection than consistent condom use but has lower risk compared with anal intercourse without a condom and without serosorting (99–101). Serosorting practices have been associated with increased risk for STIs, including chlamydia and gonorrhea (102,103).

Serosorting is not recommended for the following reasons: many MSM who have HIV infection do not know they have HIV because they have not been tested recently, men's assumptions about the HIV status of their partners might be wrong, and some men with HIV infection might not disclose or might misrepresent their HIV status. All of these factors increase

the risk that serosorting can lead to HIV infection. Serosorting has not been studied among heterosexually active persons.

## Abstinence and Reduction of Number of Sex Partners

Abstinence from oral, vaginal, and anal sex and participating in a long-term, mutually monogamous relationship with a partner known to be uninfected are prevention approaches to avoid transmission of STIs. For persons who are being treated for an STI (or whose partners are undergoing treatment), counseling that encourages abstinence from sexual intercourse until completion of the entire course of medication is vital for preventing reinfection. A trial conducted among women regarding the effectiveness of counseling messages when patients have cervicitis or vaginal discharge demonstrated that women whose sex partners have used condoms might benefit from a hierarchical message that includes condoms but women without such experience might benefit more from an abstinence-only message (104). A more comprehensive discussion of abstinence and other sexual practices that can help persons reduce their risk for STIs is available in *Contraceptive Technology, 21st Edition* (31).

## Partner Services

The term “partner services” refers to a continuum of clinical evaluation, counseling, diagnostic testing, and treatment designed to increase the number of infected persons brought to treatment and to reduce transmission among sexual networks. This continuum includes efforts of health departments, medical providers, and patients themselves. The term “public health partner services” refers to efforts by public health departments to identify the sex and needle-sharing partners of infected persons to ensure their medical evaluation and treatment. Health departments are increasingly incorporating referral to additional services, as indicated, into the partner services continuum. Aside from the general benefit to patients and partners, service referrals and linkage can mitigate the circumstances that increase risk for future STI and HIV acquisition.

The types and comprehensiveness of public health partner services and the specific STIs for which they are offered vary by public health agency, their resources, and the geographic prevalence of STIs. In most areas of the United States, health departments routinely attempt to provide partner services to all persons with infectious syphilis (primary or secondary) and persons with a new diagnosis of HIV infection. Health departments should provide partner services for persons who might have cephalosporin-resistant gonorrhea. In contrast, relatively few U.S. health departments routinely provide STI partner services to persons with gonorrhea, chlamydia,

trichomoniasis, or other STIs (105). Because STI diagnoses often can serve as risk markers for HIV acquisition (83), public health services might include follow-up of MSM with an STI to offer HIV PrEP. Public health services can also include HIV and STI prevention interventions including HIV and STI testing, linkage and relinkage of persons with HIV infection to HIV care clinics, and referral of partners of persons with STIs or HIV infection to HIV PrEP, as indicated (106–109). Clinicians should familiarize themselves with public health practices in their area; however, in most instances, providers should understand that responsibility for discussing the treatment of partners of persons with STIs rests with the diagnosing provider and the patient. State laws require a good faith effort by the provider to inform partners, and providers should familiarize themselves with public health laws.

Clinicians who do not notify partners of patients directly can still provide partner services by counseling infected persons and providing them with written information and medication to give to their partners (if recommended and allowable by state law), directly evaluating and treating sex partners, and cooperating with state and local health departments. Clinicians’ efforts to ensure treatment of patients’ sex partners can reduce the risk for reinfection and potentially diminish transmission of STIs (110). Therefore, clinicians should encourage all persons with STIs to notify their sex partners and urge them to seek medical evaluation and treatment. Exceptions to this practice include circumstances posing a risk for intimate partner violence (111). Available data are limited regarding the rate of intimate partner violence directly attributable to partner notification (112,113); however, because of the reported prevalence of intimate partner violence in the general population (114), providers should consider the potential risk before notifying partners of persons or encouraging partner notification. Time spent counseling patients about the importance of notifying partners is associated with improved notification outcomes (115). When possible, clinicians should advise persons to bring their primary sex partner with them when returning for treatment and should concurrently treat both persons. Although this approach can be effective for a main partner (116,117), it might not be a feasible approach for additional sex partners. Evidence indicates that providing patients with written information to share with sex partners can increase rates of partner treatment (110).

Certain health departments now use technology (e.g., email, texting, mobile applications, and social media outlets) to facilitate partner services for locating and notifying the sex partners of persons with STIs, including HIV (118,119). Patients now have the option to use Internet sites to send anonymous email or text messages advising partners of their exposure to an STI (120); anonymous notification via the

Internet is considered better than no notification at all. However, because the extent to which these sites affect partner notification and treatment is uncertain, patients should be encouraged to notify their partners in person or by telephone, email, or text message; alternatively, patients can authorize a medical provider or public health professional to notify their sex partners.

## Expedited Partner Therapy

Expedited partner therapy (EPT) is a harm-reduction strategy and the clinical practice of treating the sex partners of persons with diagnosed chlamydia or gonorrhea, who are unable or unlikely to seek timely treatment, by providing medications or prescriptions to the patient as allowable by law. Patients then provide partners with these therapies without the health care provider having examined the partner (<https://www.cdc.gov/std/ept>). Unless prohibited by law or other regulations, medical providers should routinely offer EPT to patients with chlamydia when the provider cannot ensure that all of a patient's sex partners from the previous 60 days will seek timely treatment. If the patient has not had sex during the 60 days before diagnosis, providers should offer EPT for the patient's most recent sex partner. Because EPT must be an oral regimen and current gonorrhea treatment involves an injection, EPT for gonorrhea should be offered to partners unlikely to access timely evaluation after linkage is explored. EPT is legal in the majority of states but varies by chlamydial or gonococcal infection. Providers should visit <https://www.cdc.gov/std/ept> to obtain updated information for their state. Providing patients with packaged oral medication is the preferred approach because the efficacy of EPT using prescriptions has not been evaluated, obstacles to EPT can exist at the pharmacy level (121,122), and many persons (especially adolescents) do not fill the prescriptions provided to them by a sex partner (123,124). Medication or prescriptions provided for EPT should be accompanied by educational materials for the partner, including treatment instructions, warnings about taking medications (e.g., if the partner is pregnant or has an allergy to the medication), general health counseling, and a statement advising that partners seek medical evaluation as soon as possible for HIV infection and any symptoms of STIs, particularly PID.

Evidence supporting EPT is based on three U.S. clinical trials involving heterosexual men and women with chlamydia or gonorrhea (125–127). All three trials reported that more partners were treated when patients were offered EPT. Two reported statistically significant decreases in the rate of reinfection, and one observed a lower risk for persistent or recurrent infection that was statistically nonsignificant. A fourth trial in the United Kingdom did not demonstrate a

difference in the risk for reinfection or in the numbers of partners treated between persons offered EPT and those advised to notify their sex partners (128). U.S. trials and a meta-analysis of EPT revealed that the magnitude of reduction in reinfection of index patients, compared with patient referral, differed according to the STI and the sex of the index patient (110,125–127). However, across trials, reductions in chlamydia prevalence at follow-up were approximately 20%, and reductions in gonorrhea were approximately 50% at follow-up.

Existing data indicate that EPT also might have a role in partner management for trichomoniasis; however, no partner management intervention has been reported to be more effective than any other in reducing trichomoniasis reinfection rates (129,130). No data support use of EPT in the routine management of patients with syphilis.

Data are limited regarding use of EPT for gonococcal or chlamydial infections among MSM, compared with heterosexuals (131,132). Published studies, including recent data regarding extragenital testing, indicated that male partners of MSM with diagnosed gonorrhea or chlamydia might have other bacterial STIs (gonorrhea or syphilis) or HIV (133–135). Studies have reported that 5% of MSM have a new diagnosis of HIV when evaluated as partners of men with gonococcal or chlamydial infections (133,134); however, more recent data indicate that, in certain settings, the frequency of HIV infection is much lower (135). Considering limited data and potential for other bacterial STIs among MSM partners, shared clinical decision-making regarding EPT is recommended. All persons who receive bacterial STI diagnoses and their sex partners, particularly MSM, should be tested for HIV, and those at risk for HIV infection should be offered HIV PrEP (<https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf>).

## Reporting and Confidentiality

Accurate and timely reporting of STIs is integral to public health efforts in assessing morbidity trends, allocating limited resources, and assisting local health authorities with partner notification and treatment. STI and HIV/AIDS cases should be reported in accordance with state and local statutory requirements. Syphilis (including congenital syphilis), gonorrhea, chlamydia, chancroid, and HIV are reportable diseases in every state. Because the requirements for reporting other STIs differ by state, clinicians should be familiar with the reporting requirements applicable within their jurisdictions.

Reporting can be provider based, laboratory based, or both. Clinicians who are unsure of state and local reporting requirements should seek advice from state or local health department STI programs. STI and HIV reports are kept confidential. In most jurisdictions, such reports are protected

by statute or regulation. Before conducting a follow-up of a person with a positive STI test result, public health professionals should consult the patient's health care provider, if possible, to inform them of the purpose of the public health visit, verify the diagnosis, determine the treatments received, and ascertain the best approaches to patient follow-up.

## Retesting After Treatment to Detect Repeat Infections

Retesting 3 months after diagnosis of chlamydia, gonorrhea, or trichomoniasis can detect repeat infection and potentially can be used to enhance population-based prevention (136,137). Any person who has a positive test for chlamydia or gonorrhea, along with women who have a positive test for trichomonas, should be rescreened 3 months after treatment. Any person who receives a syphilis diagnosis should undergo follow-up serologic syphilis testing per current recommendations and follow-up testing for HIV (see Syphilis). Additional information regarding retesting is available elsewhere in this report (see Chlamydial Infections; Gonococcal Infections; Syphilis; Trichomoniasis).

## STI Detection Among Special Populations

### Pregnant Women

Intrauterine or perinatally transmitted STIs can have debilitating effects on pregnant women, their fetuses, and their partners. All pregnant women and their sex partners should be asked about STIs, counseled about the possibility of perinatal infections, and provided access to recommended screening and treatment, if needed.

Recommendations for screening pregnant women for STIs to detect asymptomatic infections are based on disease severity and sequelae, prevalence among the population, costs, medicolegal considerations (e.g., state laws), and other factors. The following screening recommendations for pregnant women summarize clinical guidelines from federal agencies and medical professional organizations.

### Screening Recommendations

#### HIV Infection

All pregnant women in the United States should be tested for HIV at the first prenatal visit, even if they have been previously tested (138). Testing pregnant women for HIV and prompt linkage to care of women with HIV infection are vital for women's health and reducing perinatal transmission of

HIV through ART and obstetrical interventions. HIV testing should be offered as part of the routine panel of prenatal tests (i.e., opt-out testing). For women who decline HIV testing, providers should address their concerns and, when appropriate, continue to encourage testing. Partners of pregnant patients should be offered HIV testing if their status is unknown (139).

Retesting in the third trimester (preferably before 36 weeks' gestation) is recommended for women at high risk for acquiring HIV infection. Examples of women at high risk include those who inject drugs, have STIs during pregnancy, have multiple sex partners during pregnancy, have a new sex partner during pregnancy, or have partners with HIV infection; those who are receiving care in health care facilities in settings with HIV incidence  $\geq 1$  per 1,000 women per year; those who are incarcerated; those who live in areas with high rates of HIV infection; or those who have signs or symptoms of acute HIV infection (e.g., fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, oral ulcers, leukopenia, thrombocytopenia, or transaminase elevation) (140).

Rapid HIV testing should be performed for any woman in labor who has not been tested for HIV during pregnancy or whose HIV status is unknown, unless she declines. If a rapid HIV test result is positive, ART should be administered without waiting for the results of confirmatory testing (<https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf>).

#### Syphilis

During 2012–2019, congenital syphilis rates in the United States increased from 8.4 to 48.5 cases per 100,000 births, a 477.4% increase (141). At least 45 states have a prenatal syphilis testing requirement, with high variability among those requirements (142). In the United States, all pregnant women should be screened for syphilis at the first prenatal visit, even if they have been tested previously (143). Prenatal screening for syphilis has been reported to be suboptimal in the United States (144,145). Testing in the third trimester and at delivery can prevent congenital syphilis cases (146,147). Partners of pregnant women with syphilis should be evaluated, tested, and treated.

When access to prenatal care is not optimal, a stat rapid plasma reagins (RPR) card test and treatment, if that test is reactive, should be administered at the time that a pregnancy is confirmed or when the pregnancy test is performed, if follow-up is uncertain. Pregnant women should be retested for syphilis at 28 weeks' gestation and at delivery if the mother lives in a community with high syphilis rates or is at risk for syphilis acquisition during pregnancy (e.g., misuses drugs or has an STI during pregnancy, having multiple sex partners, having a new sex partner, or having a sex partner with an STI). Neonates should not be discharged from the hospital unless

the syphilis serologic status of the mother has been determined at least once during pregnancy. Any woman who delivers a stillborn infant should be tested for syphilis.

## Hepatitis B

All pregnant women should be routinely tested for hepatitis B surface antigen (HBsAg) at the first prenatal visit even if they have been previously vaccinated or tested (148). Women who are HBsAg positive should be provided with, or referred for, counseling and medical management. Women who are HBsAg negative but at risk for HBV infection should be vaccinated. Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection (e.g., having had more than one sex partner during the previous 6 months, having been evaluated or treated for an STI, having had recent or current injection drug use, or having an HBsAg-positive sex partner), and those with clinical hepatitis should be tested at the time of admission to the hospital for delivery. To avoid misinterpreting a transient positive HBsAg result during the 21 days after vaccination, HBsAg testing should be performed before vaccine administration. All laboratories that conduct HBsAg tests should test initially reactive specimens with a licensed neutralizing confirmatory test. When pregnant women are tested for HBsAg at the time of admission for delivery, shortened testing protocols can be used, and initially reactive results should prompt expedited administration of immunoprophylaxis to neonates (148). Pregnant women who are HBsAg positive should be reported to the local or state health department to ensure that they are entered into a case-management system and that timely and age-appropriate prophylaxis is provided to their infants. Information concerning the pregnant woman's HBsAg status should be provided to the hospital where delivery is planned and to the health care provider who will care for the newborn. In addition, household and sexual contacts of women who are HBsAg positive should be vaccinated.

## Chlamydia

All pregnant women aged <25 years as well as older women at increased risk for chlamydia (e.g., those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) should be routinely screened for *Chlamydia trachomatis* at the first prenatal visit (149). Pregnant women who remain at increased risk for chlamydial infection also should be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the neonate. Pregnant women identified as having chlamydia should be treated immediately and have a test of cure to document chlamydial eradication by a nucleic acid amplification test (NAAT) 4 weeks after treatment. All persons

diagnosed with a chlamydial infection should be rescreened 3 months after treatment.

## Gonorrhea

All pregnant women aged <25 years as well as women aged ≥25 years at increased risk for gonorrhea (e.g., those with other STIs during pregnancy or those with a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI or is exchanging sex for money or drugs) should be screened for *Neisseria gonorrhoeae* at the first prenatal visit (149). Pregnant women who remain at high risk for gonococcal infection also should be retested during the third trimester to prevent maternal postnatal complications and gonococcal infection in the neonate. Clinicians should consider the communities they serve and might choose to consult local public health authorities for guidance on identifying groups that are more vulnerable to gonorrhea acquisition on the basis of local disease prevalence. Gonococcal infection, in particular, is concentrated among specific geographic locations and communities (<https://www.cdc.gov/std/statistics/2019/default.htm>). Pregnant women identified as having gonorrhea should be treated immediately. All persons diagnosed with gonorrhea should be rescreened 3 months after treatment.

## Hepatitis C Virus

The rate of hepatitis C virus (HCV) infection has increased among pregnant women in recent years (150–153). HCV screening should be performed for all pregnant women during each pregnancy, except in settings where the HCV infection (HCV positivity) rate is <0.1% (154–156). The most important risk factor for HCV infection is past or current injecting drug use (157). Additional risk factors include having had a blood transfusion or organ transplantation before July 1992, having received clotting factor concentrates produced before 1987, having received an unregulated tattoo, having been on long-term hemodialysis, having other percutaneous exposures, or having HIV infection. All women with HCV infection should receive counseling, supportive care, and linkage to care (<https://www.hcvguidelines.org>). No vaccine is available for preventing HCV transmission.

## Cervical Cancer

Pregnant women should undergo cervical cancer screening and at the same frequency as nonpregnant women; however, management differs slightly during pregnancy (158). Colposcopy is recommended for the same indications during pregnancy as for nonpregnant women. However, biopsies may be deferred, and endocervical sampling should not be performed. Treatment should not be performed during pregnancy unless cancer is detected.

## Bacterial Vaginosis, Trichomoniasis, and Genital Herpes

Evidence does not support routine screening for BV among asymptomatic pregnant women at high risk for preterm delivery (159). Symptomatic women should be evaluated and treated (see Bacterial Vaginosis). Evidence does not support routine screening for *Trichomonas vaginalis* among asymptomatic pregnant women. Women who report symptoms should be evaluated and treated (see Trichomoniasis). In addition, evidence does not support routine HSV-2 serologic screening among asymptomatic pregnant women. However, type-specific serologic tests might be useful for identifying pregnant women at risk for HSV-2 infection and for guiding counseling regarding the risk for acquiring genital herpes during pregnancy. Routine serial cultures for HSV are not indicated for women in the third trimester who have a history of recurrent genital herpes.

For more detailed discussions of STI screening and treatment among pregnant women, refer to the following references: *Screening for HIV Infection: U.S. Preventive Services Task Force Recommendation Statement* (138); *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States* (<https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf>); *Guidelines for Perinatal Care* (160); *Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices* (12); *Screening for Chlamydia and Gonorrhea: U.S. Preventive Services Task Force Recommendation Statement* (149); *Screening for Bacterial Vaginosis in Pregnant Persons to Prevent Preterm Delivery: U.S. Preventive Services Task Force Recommendation Statement* (159); *Screening for Syphilis Infection in Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement* (161); *Serologic Screening for Genital Herpes Infection: U.S. Preventive Services Task Force Recommendation Statement* (162); *Screening for HIV Infection in Pregnant Women: A Systematic Review for the U.S. Preventive Services Task Force* (163); *Screening for Hepatitis B in Pregnant Women: Updated Evidence Report and Systematic Review for the U.S. Preventive Services Task Force* (164); and *CDC Recommendations for Hepatitis C Screening Among Adults — United States, 2020* (156).

## Adolescents

In the United States, prevalence rates of certain STIs are highest among adolescents and young adults (141). For example, reported rates of chlamydia and gonorrhea are highest among females during their adolescent and young adult years, and many persons acquire HPV infection during that time.

Persons who initiate sex early in adolescence are at higher risk for STIs, as are adolescents living in detention facilities; those receiving services at STD clinics; those who are involved in commercial sex exploitation or survival sex and are exchanging sex for drugs, money, food, or housing; young males who have sex with males (YMSM); transgender youths; and youths with disabilities, substance misuse, or mental health disorders. Factors contributing to increased vulnerability to STIs during adolescence include having multiple sex partners, having sequential sex partnerships of limited duration or concurrent partnerships, failing to use barrier protection consistently and correctly, having lower socioeconomic status, and facing multiple obstacles to accessing health care (141,165).

All 50 states and the District of Columbia explicitly allow minors to consent for their own STI services. No state requires parental consent for STI care, although the age at which a minor can provide consent for specified health care services (i.e., HPV vaccination and HIV testing and treatment) varies among states. In 2019, a total of 18 states allowed but did not require physicians to notify parents of a minor's receipt of STI services, including states where minors can legally provide their own consent to the service (<https://www.cdc.gov/hiv/policies/law/states/minors.html>).

Protecting confidentiality for STI care, particularly for adolescents enrolled in private health insurance plans, presents multiple problems. After a claim has been submitted, many states mandate that health plans provide a written statement to the beneficiary indicating the service performed, the charges covered, what the insurer allows, and the amount for which the patient is responsible (i.e., explanation of benefits [EOB]) (166–169). In addition, federal laws obligate notices to beneficiaries when claims are denied, including alerting beneficiaries who need to pay for care until the allowable deductible is reached. For STI testing and treatment-related care, an EOB or medical bill that is received by a parent might disclose services provided and list STI laboratory tests performed or treatment administered. Some states have instituted mechanisms for protecting adolescents' confidentiality and limiting EOBS. Additional risks to confidentiality breaches can inadvertently occur through electronic health records, although technology continues to evolve to assist with ensuring confidential care. AAP and the Society for Adolescent Health and Medicine (SAHM) have published guidance on strategies to address emerging risks for confidentiality breaches associated with health information technology (169).

AAP and the SAHM recommend that providers have time alone with their adolescent patients that includes assessment for sexual behavior. The AAP recommendations are available at <https://services.aap.org/en/news-room/campaigns-and-toolkits/adolescent-health-care> and the SAHM

recommendations are available at <https://www.adolescenthealth.org/My-SAHM/Login-or>Create-an-Account.aspx?returnurl=%2fResources%2fClinical-Care-Resources%2fConfidentiality.aspx>. Discussions concerning sexual behavior should be tailored for the patient's developmental level and be aimed at identifying risk behaviors (e.g., multiple partners; oral, anal, or vaginal sex; or drug misuse behaviors). Careful, nonjudgmental, and thorough counseling is particularly vital for adolescents who might not feel comfortable acknowledging their engagement in behaviors that make them more vulnerable to acquiring STIs.

## Screening Recommendations

Recommendations for screening adolescents for STIs to detect asymptomatic infections are based on disease severity and sequelae, prevalence among the population, costs, medicolegal considerations (e.g., state laws), and other factors. Routine laboratory screening for common STIs is indicated for all sexually active adolescents. The following screening recommendations summarize published clinical prevention guidelines for sexually active adolescents from federal agencies and medical professional organizations.

### Chlamydia

Routine screening for *C. trachomatis* infection on an annual basis is recommended for all sexually active females aged <25 years (149). Rectal chlamydial testing can be considered for females on the basis of reported sexual behaviors and exposure, through shared clinical decision-making between the patient and the provider (170,171). Evidence is insufficient to recommend routine screening for *C. trachomatis* among sexually active young males, on the basis of efficacy and cost-effectiveness. However, screening of sexually active young males should be considered in clinical settings serving populations of young men with a high prevalence of chlamydial infections (e.g., adolescent service clinics, correctional facilities, and STD clinics). Chlamydia screening, including pharyngeal or rectal testing, should be offered to all YMSM at least annually on the basis of sexual behavior and anatomic site of exposure (see Men Who Have Sex with Men).

### Gonorrhea

Routine screening for *N. gonorrhoeae* on an annual basis is recommended for all sexually active females aged <25 years (149). Exogenous gonorrhea screening (pharyngeal or rectal) can be considered for females on the basis of reported sexual behaviors and exposure, through shared clinical-decision between the patient and the provider (170,171). Gonococcal infection is more prevalent among certain geographic locations and communities (141). Clinicians should consider the communities they serve and consult local public health

authorities for guidance regarding identifying groups that are more vulnerable to gonorrhea acquisition on the basis of local disease prevalence. Evidence is insufficient to recommend routine screening, on the basis of efficacy and cost-effectiveness, for *N. gonorrhoeae* among asymptomatic sexually active young males who have sex with females only. Screening for gonorrhea, including pharyngeal or rectal testing, should be offered to YMSM at least annually (see Men Who Have Sex with Men).

Providers might consider opt-out chlamydia and gonorrhea screening (i.e., the patient is notified that testing will be performed unless the patient declines, regardless of reported sexual activity) for adolescent and young adult females during clinical encounters. Cost-effectiveness analyses indicate that opt-out chlamydia screening among adolescent and young adult females might substantially increase screening, be cost-saving (172), and identify infections among patients who do not disclose sexual behavior (173).

### HIV Infection

HIV screening should be discussed and offered to all adolescents. Frequency of repeat screenings should be based on the patient's sexual behaviors and the local disease prevalence (138). Persons with HIV infection should receive prevention counseling and linkage to care before leaving the testing site.

### Cervical Cancer

Guidelines from USPSTF and ACOG recommend that cervical cancer screening begin at age 21 years (174,175). This recommendation is based on the low incidence of cervical cancer and limited usefulness of screening for cervical cancer among adolescents (176). In contrast, the 2020 ACS guidelines recommend that cervical cancer screening begin at age 25 years with HPV testing. This change is recommended because the incidence of invasive cervical cancer in women aged <25 years is decreasing because of vaccination (177). Adolescents with HIV infection who have initiated sexual intercourse should have cervical screening cytology in accordance with HIV/AIDS guidelines (<https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/human-papillomavirus-disease?view=full>).

### Other Sexually Transmitted Infections

YMSM and pregnant females should be routinely screened for syphilis (see Pregnant Women; Men Who Have Sex with Men). Local disease prevalence can help guide decision-making regarding screening for *T. vaginalis*, especially among adolescent females in certain areas. Routine screening of adolescents and young adults who are asymptomatic for certain STIs (e.g., syphilis, trichomoniasis, BV, HSV, HAV, and HBV) is not typically recommended.

## Primary Prevention Recommendations

Primary prevention and anticipatory guidance for recognizing symptoms and behaviors associated with STIs are strategies that should be incorporated into all types of health care visits for adolescents and young adults. The following recommendations for primary prevention of STIs (i.e., vaccination and counseling) are based on published clinical guidelines for sexually active adolescents and young adults from federal agencies and medical professional organizations.

- HPV vaccination is recommended through age 26 years for those not vaccinated previously at the routine age of 11 or 12 years (<https://www.cdc.gov/vaccines/hcp/acip-recoms/vacc-specific/hpv.html>).
- The HBV vaccination series is recommended for all adolescents and young adults who have not previously received the universal HBV vaccine series during childhood (12).
- The HAV vaccination series should be offered to adolescents and young adults as well as those who have not previously received the universal HAV vaccine series during childhood (<https://www.cdc.gov/vaccines/schedules/hcp/imz-child-indications.html#note-hepa>).
- Information regarding HIV transmission, prevention, testing, and implications of infection should be regarded as an essential component of the anticipatory guidance provided to all adolescents and young adults as part of routine health care.
- CDC and USPSTF recommend offering HIV PrEP to adolescents weighing  $\geq 35$  kg and adults who are HIV negative and at substantial risk for HIV infection (80,178). YMSM should be offered PrEP in youth-friendly settings with tailored adherence support (e.g., text messaging and visits per existing guidelines). Indications for PrEP, initial and follow-up prescribing guidance, and laboratory testing recommendations are the same for adolescents and adults (<https://www.cdc.gov/hiv/risk/prep>).
- Medical providers who care for adolescents and young adults should integrate sexuality education into clinical practice. Health care providers should counsel adolescents about the sexual behaviors that are associated with risk for acquiring STIs and should educate patients regarding evidence-based prevention strategies, which includes a discussion about abstinence and other risk-reduction behaviors (e.g., consistent and correct condom use and reduction in the number of sex partners including concurrent partners). Interactive counseling approaches (e.g., patient-centered counseling and motivational interviewing) are effective STI and HIV prevention strategies and are recommended by USPSTF. Educational materials (e.g., handouts, pamphlets, and videos) can reinforce office-based educational efforts.

## Children

Management of children who have STIs requires close cooperation among clinicians, laboratorians, and child-protection authorities. Official investigations, when indicated, should be initiated promptly. Certain diseases (e.g., gonorrhea, syphilis, HIV, chlamydia, and trichomoniasis), if acquired after the neonatal period, strongly indicate sexual contact. For other diseases (e.g., HSV, HPV and anogenital warts, and vaginitis), the association with sexual contact is not as clear (see Sexual Assault and Abuse and STIs).

## Men Who Have Sex with Men

MSM comprise a diverse group in terms of behaviors, identities, and health care needs (179). The term “MSM” often is used clinically to refer to sexual behavior alone, regardless of sexual orientation (e.g., a person might identify as heterosexual but still be classified as MSM). Sexual orientation is independent of gender identity. Classification of MSM can vary in the inclusion of transgender men and women on the basis of whether men are defined by sex at birth (i.e., transgender women included) or current gender identity (i.e., transgender men included). Therefore, sexual orientation as well as gender identity of individual persons and their sex partners should be obtained during health care visits. MSM might be at increased risk for HIV and other STIs because of their sexual network or behavioral or biologic factors, including number of concurrent partners, condomless sex, anal sex, or substance use (180–182). These factors, along with sexual network or higher community disease prevalence, can increase the risk for STIs among MSM compared with other groups (183,184).

Performing a detailed and comprehensive sexual history is the first step in identifying vulnerability and providing tailored counseling and care (3). Factors associated with increased vulnerability to STI acquisition among MSM include having multiple partners, anonymous partners, and concurrent partners (185,186). Repeat syphilis infections are common and might be associated with HIV infection, substance use (e.g., methamphetamines), Black race, and multiple sex partners (187). Similarly, gonorrhea incidence has increased among MSM and might be more likely to display antimicrobial resistance compared with other groups (188,189). Gonococcal infection among MSM has been associated with similar risk factors to syphilis, including having multiple anonymous partners and substance use, especially methamphetamines (190). Disparities in gonococcal infection are also more pronounced among certain racial and ethnic groups of MSM (141).

## HIV Risk Among Men Who Have Sex with Men

MSM are disproportionately at risk for HIV infection. In the United States, the estimated lifetime risk for HIV infection among MSM is one in six, compared with heterosexual men at one in 524 and heterosexual women at one in 253 (191). These disparities are further exacerbated by race and ethnicity, with African American/Black and Hispanic/Latino MSM having a one in two and a one in four lifetime risk for HIV infection, respectively. For HIV, transmission occurs much more readily through receptive anal sex, compared with penile-vaginal sex (192). Similar to other STIs, multiple partners, anonymous partners, condomless sex, and substance use are all associated with HIV infection (193–196). Importantly, other STIs also might significantly increase the risk for HIV infection (197–199). An estimated 10% of new HIV infections were attributable to chlamydial or gonococcal infection (81). A substantial number of MSM remain unaware of their HIV diagnosis (200). Clinical care involving MSM, including those who have HIV infection, should involve asking about STI-related risk factors and routine STI testing. Clinicians should routinely ask MSM about their sexual behaviors and symptoms consistent with common STIs, including urethral discharge, dysuria, ulcers, rash, lymphadenopathy, and anorectal symptoms that might be consistent with proctitis (e.g., discharge, rectal bleeding, pain on defecation, or pain during anal sex). However, certain STIs are asymptomatic, especially at rectal and pharyngeal sites, and routine testing is recommended. In addition, clinicians should provide education and counseling regarding evidence-based safer-sex approaches that have demonstrated effectiveness in reducing STI incidence (see HIV Infection, Detection, Counseling, and Referral).

## Pre-Exposure Prophylaxis for HIV Prevention

PrEP is the use of medications for preventing an infection before exposure. Studies have demonstrated that a daily oral medication TDF/FTC is effective in preventing HIV acquisition, and specifically among MSM (74,75,201). PrEP guidelines provide information regarding sexually active persons who are at substantial risk for acquiring HIV infection (having had anal or vaginal sex during the previous 6 months with either a partner with HIV infection, a bacterial STI in the past 6 months, or inconsistent or no condom use with a sex partner) or persons who inject drugs (injecting partner with HIV infection or sharing injection equipment) (80). Those guidelines provide information regarding daily PrEP use for either TDF/FTC (men or women) or tenofovir alafenamide and emtricitabine for MSM. Screening for bacterial STIs should occur at least every 6 months for all sexually active patients and every 3 months among MSM or

among patients with ongoing risk behaviors. MSM taking PrEP might compensate for decreased HIV acquisition risk by using condoms less frequently or modifying their behavior in other ways (202,203), although data regarding this behavior are inconsistent. Studies have reported that MSM taking PrEP have high rates of STIs, and frequent screening is warranted (204–206).

## Importance of Rectal and Pharyngeal Testing

Rectal and pharyngeal testing by NAAT for gonorrhea and chlamydia is recognized as an important sexual health consideration for MSM. Rectal gonorrhea and chlamydia are associated with HIV infection (82,207), and men with repeat rectal infections can be at substantially higher risk for HIV acquisition (208). Pharyngeal infections with gonorrhea or chlamydia might be a principal source of urethral infections (209–211). Studies have demonstrated that among MSM, prevalence of rectal gonorrhea and chlamydia ranges from 0.2% to 24% and 2.1% to 23%, respectively, and prevalence of pharyngeal gonorrhea and chlamydia ranges from 0.5% to 16.5% and 0% to 3.6%, respectively (171). Approximately 70% of gonococcal and chlamydial infections might be missed if urogenital-only testing is performed among MSM (212–216) because most pharyngeal and rectal infections are asymptomatic. Self-collected swabs have been reported to be an acceptable means of collection for pharyngeal and rectal specimens (217–219), which can enhance patient comfort and reduce clinical workloads.

A detailed sexual history should be taken for all MSM to identify anatomic locations exposed to infection for screening. Clinics that provide services for MSM at high risk should consider implementing routine extragenital screening for *N. gonorrhoeae* and *C. trachomatis* infections, and screening is likely to be cost-effective (220).

## Screening Recommendations

STI screening among MSM has been reported to be suboptimal. In a cross-sectional sample of MSM in the United States, approximately one third reported not having had an STI test during the previous 3 years, and MSM with multiple sex partners reported less frequent screening (221). MSM living with HIV infection and engaged in care also experience suboptimal rates of STI testing (222,223). Limited data exist regarding the optimal frequency of screening for gonorrhea, chlamydia, and syphilis among MSM, with the majority of evidence derived from mathematical modeling. Models from Australia have demonstrated that increasing syphilis screening frequency from two times a year to four times a year resulted in a relative decrease of 84% from peak prevalence (224). In a compartmental model applied to different populations in Canada, quarterly syphilis screening averted more than twice

the number of syphilis cases, compared with semiannual screening (225). Furthermore, MSM screening coverage needed for eliminating syphilis among a population is substantially reduced from 62% with annual screening to 23% with quarterly screening (226,227). In an MSM transmission model that explored the impact of HIV PrEP use on STI prevalence, quarterly chlamydia and gonorrhea screening was associated with an 83% reduction in incidence (205). The only empiric data available that examined the impact of screening frequency come from an observational cohort of MSM using HIV PrEP in which quarterly screening identified more bacterial STIs, and semiannual screening would have resulted in delayed treatment of 35% of total identified STI infections (206). In addition, quarterly screening was reported to have prevented STI exposure in a median of three sex partners per STI infection (206). On the basis of available evidence, quarterly screening for gonorrhea, chlamydia, and syphilis for certain sexually active MSM can improve case finding, which can reduce the duration of infection at the population level, reduce ongoing transmission and, ultimately, prevalence among this population (228).

Preventive screening for common STIs is indicated for all MSM. The following screening recommendations summarize published federal agency and USPSTF clinical prevention guidelines for MSM and should be performed at least annually.

### HIV Infection

HIV serologic testing is indicated if HIV status is unknown or if HIV negative and the patient or their sex partner has had more than one sex partner since the most recent HIV test.

### Syphilis

Syphilis serologic testing is indicated to establish whether persons with reactive tests have untreated syphilis, have partially treated syphilis, or are manifesting a slow or inadequate serologic response to recommended previous therapy.

### Gonorrhea and Chlamydia

The following testing is recommended for MSM:

- A test for urethral infection\* with *N. gonorrhoeae* and *C. trachomatis* among men who have had insertive intercourse during the preceding year (urine NAAT is preferred).
- A test for rectal infection\* with *N. gonorrhoeae* and *C. trachomatis* among men who have had receptive anal intercourse during the preceding year (rectal NAAT is preferred).

\* Regardless of condom use during exposure.

- A test for pharyngeal infection\* with *N. gonorrhoeae* among men who have had receptive oral intercourse during the preceding year (pharyngeal NAAT is preferred).
- Testing for *C. trachomatis* pharyngeal infection is not recommended.

Basing screening practices solely on history might be suboptimal because providers might feel uncomfortable taking a detailed sexual history (229), men might also feel uncomfortable sharing personal sexual information with their provider, and rectal and pharyngeal infections can be identified even in the absence of reported risk behaviors (171). Furthermore, the role of saliva, kissing, and rimming (i.e., oral-rectal contact) in the transmission of *N. gonorrhoeae* and *C. trachomatis* has not been well studied (230–232).

Rectal and pharyngeal testing (provider-collected or self-collected specimens) should be performed for all MSM who report exposure at these sites. Testing can be offered to MSM who do not report exposure at these sites after a detailed explanation, due to known underreporting of risk behaviors. All MSM with HIV infection entering care should be screened for gonorrhea and chlamydia at appropriate anatomic sites of exposure as well as for syphilis.

More frequent STI screening (i.e., for syphilis, gonorrhea, and chlamydia) at 3- to 6-month intervals is indicated for MSM, including those taking PrEP and those with HIV infection, if risk behaviors persist or if they or their sex partners have multiple partners. In addition, providers can consider the benefits of offering more frequent HIV screening (e.g., every 3–6 months) to MSM at increased risk for acquiring HIV infection.

### Hepatitis B Virus

All MSM should be screened with HBsAg, HBV core antibody, and HBV surface antibody testing to detect HBV infection (233). Vaccination against both HAV and HBV is recommended for all MSM for whom previous infection or vaccination cannot be documented. Serologic testing can be considered before vaccinating if the patient's vaccination history is unknown; however, vaccination should not be delayed. Vaccinating persons who have had previous infection or vaccination does not increase the risk for vaccine-related adverse events (see Hepatitis A Virus; Hepatitis B Virus).

### Hepatitis C Virus

CDC recommends HCV screening at least once for all adults aged ≥18 years, except in settings where the prevalence of HCV infection (HCV RNA positivity) is <0.1% (156). The American Association for the Study of Liver Diseases/Infectious Diseases Society of America guidelines recommend all MSM with HIV infection be screened for HCV during the

initial HIV evaluation and at least annually thereafter (<https://www.hcvguidelines.org>). More frequent screening depends on ongoing risk behaviors, high-risk sexual behavior, and concomitant ulcerative STIs or STI-related proctitis. Sexual transmission of HCV can occur and is most common among MSM with HIV infection (234–237). Screening for HCV in this setting is cost-effective (238,239). Screening should be performed by using HCV antibody assays followed by HCV RNA testing for those with a positive antibody test. Suspicion for acute HCV infection (e.g., clinical evidence of hepatitis and risk behaviors) should prompt consideration for HCV RNA testing, despite a negative antibody test.

### **Human Papillomavirus**

HPV infection and associated conditions (e.g., anogenital warts and anal squamous intraepithelial lesions) are highly prevalent among MSM. The HPV vaccination is recommended for all men, including MSM and transgender persons or immunocompromised males, including those with HIV infection, through age 26 years (11). More information is available at <https://www.cdc.gov/hpv/downloads/9vhpv-guidance.pdf>.

A digital anorectal examination (DARE) should be performed to detect early anal cancer among persons with HIV and MSM without HIV but who have a history of receptive anal intercourse. Data are insufficient to recommend routine anal cancer screening with anal cytology in populations at risk for anal cancer (see Anal Cancer). Health centers that initiate a cytology-based screening program should only do so if referrals to high-resolution anoscopy (HRA) and biopsy are available.

### **Herpes Simplex Virus-2**

Evaluation for HSV-2 infection with type-specific serologic tests also can be considered if infection status is unknown among persons with previously undiagnosed genital tract infection (see Genital Herpes).

### **Postexposure Prophylaxis and Pre-Exposure Prophylaxis for STI Prevention**

Studies have reported that a benefit might be derived from STI PEP and PrEP for STI prevention. One study demonstrated that monthly oral administration of a 1-g dose of azithromycin reduced infection with *N. gonorrhoeae* and *C. trachomatis* but did not decrease the incidence of HIV transmission (240). Among MSM, doxycycline taken as PEP in a single oral dose ≤24 hours after sex decreased infection with *Treponema pallidum* and *C. trachomatis*; however, no substantial effect was observed for infection with *N. gonorrhoeae* (93). Doxycycline taken as STI PrEP as 100 mg orally once daily also demonstrated a substantial reduction in gonorrhea,

chlamydia, and syphilis among MSM (90). However, these studies had limitations because of small sample size, short duration of therapy, and concerns about antibiotic resistance, specifically regarding *N. gonorrhoeae* (241). Further study is needed to determine the effectiveness of using antimicrobials for STI PrEP or PEP.

### **Counseling and Education Approaches**

Different counseling and STI prevention strategies are needed to effectively engage different groups of MSM. Outreach efforts should be guided by local surveillance efforts and community input. Engaging MSM at risk through social media, specifically online hookup sites, is an important outreach effort to consider. Hookup sites are Internet sites and mobile telephone applications that men might use for meeting other men for sex. Internet use might facilitate sexual encounters and STI transmission among MSM, and many men report using hookup sites to meet partners (242–245). The ease and accessibility of meeting partners online might reduce stigma and barriers of meeting partners through other settings. Moreover, these sites offer an opportunity for effective STI prevention messaging (246), although the cost might be limiting (247). Different groups of MSM might use different hookup sites, and efforts should be guided by local community input. Studies have demonstrated the acceptability and feasibility of reaching MSM through these hookup sites to promote STI prevention efforts (248,249).

### **Enteric Infections Among Men Who Have Sex with Men**

The importance of sexual transmission of enteric pathogens among MSM has been recognized since the 1970s, after the first report of MSM-associated shigellosis was reported in San Francisco (250,251). Global increases in the incidence of shigellosis among adult MSM have been more recently observed (252–256). Sporadic outbreaks of *Shigella sonnei* and *Shigella flexneri* have been reported among MSM (257–262). Transmission occurs through oral-anal contact or sexual contact, and transmission efficiency is enhanced by both biologic or host and behavioral factors. HIV without viral suppression can be an independent risk factor that can contribute to transmission by increasing shedding of the enteric pathogen, increasing susceptibility of the host, or both (255,263). Surveillance data in England during 2004–2015 demonstrated that 21% of nontravel-associated *Shigella* diagnoses among MSM were among persons with HIV infection (255).

Other enteric organisms might also cause disease among MSM through sexual activities leading to oral-anal contact, including bacteria such as *Escherichia coli* (264) and

*Campylobacter jejuni* or *Campylobacter coli* (265,266); viruses such as HAV (267); and parasites such as *Giardia lamblia* or *Entamoeba histolytica* (268,269). Behavioral characteristics associated with the sexual transmission of enteric infections are broadly similar to those associated with other STIs (e.g., gonorrhea, syphilis, and lymphogranuloma venereum [LGV]). This includes multiple sex partners and online hookup sites that increase opportunities for sexual mixing, which might create dense sexual networks that facilitate STI transmission among MSM (270). Specific behaviors associated with sexually transmitted enteric infections among MSM involve attendance at sex parties and recreational drug use including chem sex (i.e., using crystal methamphetamine, gamma-butyrolactone, or mephedrone before or during sex), which might facilitate condomless sex, group sex, fisting, use of sex toys, and scat play (253,271). The growing number of sexually transmitted enteric infections might be attributable in part to the emergence of antimicrobial resistance. This is well reported regarding *Shigella* species, for which rapid intercontinental dissemination of a *S. flexneri* 3a lineage with high-level resistance to azithromycin through sexual transmission among MSM (272) and clusters of multidrug resistant shigella cases among MSM have recently been reported (273). Multidrug-resistant *Campylobacter* species have also been documented (266,274). For MSM patients with diarrhea, clinicians should request laboratory examinations, including stool culture; provide counseling about the risk for infection with enteric pathogens during sexual activity (oral-anal, oral-genital, anal-genital, and digital-anal contact) that could expose them to enteric pathogens; and choose treatment, when needed, according to antimicrobial drug susceptibility.

## Women Who Have Sex with Women and Women Who Have Sex with Women and Men

WSW and WSWM comprise diverse groups with variations in sexual identity, practices, and risk behaviors. Studies indicate that certain WSW, particularly adolescents, young women, and WSWM, might be at increased risk for STIs and HIV on the basis of reported risk behaviors (275–280). Studies have highlighted the diversity of sexual practices and examined use of protective or risk-reduction strategies among WSW populations (281–283). Use of barrier protection with female partners (e.g., gloves during digital-genital sex, external condoms with sex toys, and latex or plastic barriers [also known as dental dams for oral-genital sex]) was infrequent in all studies. Although health organizations have online materials directed to patients, few comprehensive and reliable resources of sexual health information for WSW are available (284).

Recent studies regarding STI rates among WSW and WSWM indicate that WSWM experience higher rates of STIs than WSW, with rates comparable with women who have sex with men (WSM) in all studies reviewed (279,285,286). These studies indicate that WSW might experience STIs at lower rates than WSWM and WSM, although still at significant rates (287). One study reported higher sexual-risk behaviors among adolescent WSWM and WSW than among adolescent WSM (280). WSW report reduced knowledge of STI risks (288), and both WSW and WSWM experience barriers to care, especially Black WSW and WSWM (289,290). In addition, a continuum of sexual behaviors reported by WSW and WSWM indicates the need for providers to not assume lower risk for WSW, highlighting the importance of an open discussion about sexual health.

Few data are available regarding the risk for STIs conferred by sex between women; however, transmission risk probably varies by the specific STI and sexual practice (e.g., oral-genital sex; vaginal or anal sex using hands, fingers, or penetrative sex items; and oral-anal sex) (291,292). Practices involving digital-vaginal or digital-anal contact, particularly with shared penetrative sex items, present a possible means for transmission of infected cervicovaginal or anal secretions. This possibility is most directly supported by reports of shared trichomonas infections (293,294) and by concordant drug-resistance genotype testing and phylogenetic linkage analysis identifying HIV transmitted sexually between women (295,296). The majority of WSW (53%–97%) have had sex with men in the past and continue to do so, with 5%–28% of WSW reporting male partners during the previous year (292,297–300).

HPV can be transmitted through skin-to-skin contact, and sexual transmission of HPV likely occurs between WSW (301–303). HPV DNA has been detected through polymerase chain reaction (PCR)-based methods from the cervix, vagina, and vulva among 13%–30% of WSW (301,302) and can persist on fomites, including sex toys (304). Among WSW who report no lifetime history of sex with men, 26% had antibodies to HPV-16, and 42% had antibodies to HPV-6 (301). High-grade squamous intraepithelial lesions (HSIL) and low-grade squamous intraepithelial lesions (LSIL) have been detected on Papanicolaou smears (Pap tests) among WSW who reported no previous sex with men (301,302). WSWM are at risk for acquiring HPV from both their female partners and male partners and thus are at risk for cervical cancer. Therefore, routine cervical cancer screening should be offered to all women, regardless of sexual orientation or practices, and young adult WSW and WSWM should be offered HPV vaccination in accordance with recommendations (11) (<https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html>).

Genital transmission of HSV-2 between female sex partners is inefficient but can occur. A U.S. population-based survey among women aged 18–59 years demonstrated an HSV-2 seroprevalence of 30% among women reporting same-sex partners during the previous year, 36% among women reporting same-sex partners in their lifetime, and 24% among women reporting no lifetime same-sex behavior (299). HSV-2 seroprevalence among women self-identifying as homosexual or lesbian was 8%, similar to a previous clinic-based study of WSW (299,305) but was 26% among Black WSW in one study (287). The relatively frequent practice of orogenital sex among WSW and WSWM might place them at higher risk for genital infection with HSV-1, a hypothesis supported by the recognized association between HSV-1 seropositivity and previous number of female partners. Thus, sexual transmission of HSV-1 and HSV-2 can occur between female sex partners. This information should be communicated to women as part of sexual health counseling.

Trichomonas is a relatively common infection among WSW and WSWM, with prevalence rates higher than for chlamydia or gonorrhea (306,307), and direct transmission of trichomonas between female partners has been demonstrated (293,294).

Limited information is available regarding transmission of bacterial STIs between female partners. Transmission of syphilis between female sex partners, probably through oral sex, has been reported. Although the rate of transmission of *C. trachomatis* or *N. gonorrhoeae* between women is unknown, infection also might be acquired from past or current male partners. Data indicate that *C. trachomatis* infection among WSW can occur (275,286,308,309). Data are limited regarding gonorrhea rates among WSW and WSWM (170). Reports of same-sex behavior among women should not deter providers from offering and providing screening for STIs, including chlamydia, according to guidelines.

BV is common among women, and even more so among women with female partners (310–312). Epidemiologic data strongly demonstrate that BV is sexually transmitted among women with female partners. Evidence continues to support the association of such sexual behaviors as having a new partner, having a partner with BV, having receptive oral sex, and having digital-vaginal and digital-anal sex with incident BV (313,314). A study including monogamous couples demonstrated that female sex partners frequently share identical genital *Lactobacillus* strains (315). Within a community-based cohort of WSW, extravaginal (i.e., oral and rectal) reservoirs of BV-associated bacteria were a risk factor for incident BV (316). Studies have examined the impact of specific sexual practices on the vaginal microflora (306,317–319) and on recurrent (320) or incident (321,322) BV among WSW. A BV pathogenesis study in WSW reported that *Prevotella bivia*,

*Gardnerella vaginalis*, and *Atopobium vaginae* might have substantial roles in development of incident BV (323). These studies have continued to support, although have not proven, the hypothesis that sexual behaviors, specific BV-associated bacteria, and possibly exchange of vaginal or extravaginal microbiota (e.g., oral bacterial communities) between partners might be involved in the pathogenesis of BV among WSW.

Although BV is common among WSW, routine screening for asymptomatic BV is not recommended. Results of one randomized trial used a behavioral intervention to reduce persistent BV among WSW through reduced sharing of vaginal fluid on hands or sex toys. Women randomly assigned to the intervention were 50% less likely to report receptive digital-vaginal contact without gloves than control subjects, and they reported sharing sex toys infrequently. However, these women had no reduction in persistent BV at 1 month posttreatment and no reduction in incident episodes of recurrent BV (324). Trials have not been reported examining the benefits of treating female partners of women with BV. Recurrent BV among WSW is associated with having a same-sex partner and a lack of condom use (325). Increasing awareness of signs and symptoms of BV among women and encouraging healthy sexual practices (e.g., avoiding shared sex toys, cleaning shared sex toys, and using barriers) might benefit women and their partners.

Sexually active women are at risk for acquiring bacterial, viral, and protozoal STIs from current and previous partners, both male and female. WSW should not be presumed to be at low or no risk for STIs on the basis of their sexual orientation. Report of same-sex behavior among women should not deter providers from considering and performing screening for STIs and cervical cancer according to guidelines. Effective screening requires that care providers and their female patients engage in a comprehensive and open discussion of sexual and behavioral risks that extends beyond sexual identity.

## Transgender and Gender Diverse Persons

Transgender persons often experience high rates of stigma and socioeconomic and structural barriers to care that negatively affect health care usage and increase susceptibility to HIV and STIs (326–332). Persons who are transgender have a gender identity that differs from the sex that they were assigned at birth (333,334). Transgender women (also known as trans women, transfeminine persons, or women of transgender experience) are women who were assigned male sex at birth (born with male anatomy). Transgender men (also known as trans men, transmasculine persons, or men of transgender experience) are men who were assigned female sex at birth (i.e., born with female anatomy). In addition, certain persons might identify outside the gender binary of male or female or move back and

forth between different gender identities and use such terms as “gender nonbinary,” “genderqueer,” or “gender fluid” to describe themselves. Persons who use terms such as “agender” or “null gender” do not identify with having any gender. The term “cisgender” is used to describe persons who identify with their assigned sex at birth. Prevalence studies of transgender persons among the overall population have been limited and often are based on small convenience samples.

Gender identity is independent of sexual orientation. Sexual orientation identities among transgender persons are diverse. Persons who are transgender or gender diverse might have sex with cisgender men, cisgender women, or other transgender or gender nonbinary persons.

## Clinical Environment Assessment

Providers should create welcoming environments that facilitate disclosure of gender identity and sexual orientation. Clinics should document gender identity and sex assigned at birth for all patients to improve sexual health care for transgender and gender nonbinary persons. Assessment of gender identity and sex assigned at birth has been validated among diverse populations, has been reported to be acceptable (335,336), and might result in increased patients identifying as transgender (337).

Lack of medical provider knowledge and other barriers to care (e.g., discrimination in health care settings or denial of services) often result in transgender and gender nonbinary persons avoiding or delaying preventive care services (338–340) and incurring missed opportunities for HIV and STI prevention services. Gender-inclusive and trauma-guided health care might increase the number of transgender patients who seek sexual health services, including STI testing (341), because transgender persons are at high risk for sexual violence (342).

Primary care providers should take a comprehensive sexual history, including a discussion of STI screening, HIV PrEP and PEP, behavioral health, and social determinants of sexual health. Clinicians can improve the experience of sexual health screening and counseling for transgender persons by asking for their choice of terminology or modifying language (e.g., asking patients their gender pronouns) to be used during clinic visits and history taking and examination (343). Options for fertility preservation, pregnancy potential, and contraception options should also be discussed, if indicated. For transgender persons who retain a uterus and ovaries, ovulation might continue in the presence of testosterone therapy, and pregnancy potential exists (<https://transcare.ucsf.edu>).

## Transgender Women

A systematic review and meta-analysis of HIV infection among transgender women estimated that HIV prevalence in

the United States is 14% among transgender women, with the highest prevalence among Black (44%) and Hispanic (26%) transgender women (344). Data also demonstrate high rates of HIV infection among transgender women worldwide (345). Bacterial STI prevalence varies among transgender women and is based largely on convenience samples. Despite limited data, international and U.S. studies have indicated elevated incidence and prevalence of gonorrhea and chlamydia among transgender women similar to rates among cisgender MSM (346–348). A recent study using data from the STD Surveillance Network revealed that the proportions of transgender women with extragenital chlamydial or gonococcal infections were similar to those of cisgender MSM (349).

Providers caring for transgender women should have knowledge of their patients’ current anatomy and patterns of sexual behavior before counseling them about STI and HIV prevention. The majority of transgender women have not undergone genital-affirmation surgery and therefore might retain a functional penis; in these instances, they might engage in insertive oral, vaginal, or anal sex as well as receptive oral or anal sex. In the U.S. Transgender Survey, 12% of transgender women had undergone vaginoplasty surgery, and approximately 50% more were considering surgical intervention (350). Providers should have knowledge about the type of tissue used to construct the neovagina, which can affect future STI and HIV preventive care and screening recommendations. The majority of vaginoplasty surgeries conducted in the United States use penile and scrotal tissue to create the neovagina (351). Other surgical techniques use intestinal tissue (e.g., sigmoid colon graft) or split-skin grafts (352). Although these surgeries involve penectomy and orchectomy, the prostate remains intact. Transgender women who have had a vaginoplasty might engage in receptive vaginal, oral, or anal sex.

Neovaginal STIs have infrequently been reported in the literature and include HSV and HPV/genital warts in penile-inversion vaginoplasty, *C. trachomatis* in procedures that involved penile skin and grafts with urethra mucosa or abdominal peritoneal lining (353), and *N. gonorrhoeae* in both penile-inversion and colovaginoplasty (354–359). If the vaginoplasty used an intestinal graft, a risk also exists for bowel-related disease (e.g., adenocarcinoma, inflammatory bowel disease, diversion colitis, and polyps) (360–362).

## Transgender Men

The few studies of HIV prevalence among transgender men indicated that they have a lower prevalence of HIV infection than transgender women. A recent estimate of HIV prevalence among transgender men was 2% (344). However, transgender men who have sex with cisgender men might be at elevated

risk for HIV infection (332,363,364). Data are limited regarding STI prevalence among transgender men, and the majority of studies have used clinic-based data or convenience sampling. Recent data from the STD Surveillance Network demonstrated higher prevalence of gonorrhea and chlamydia among transgender men, similar to rates reported among cisgender MSM (365).

The U.S. Transgender Survey indicated that the proportion of transgender men and gender diverse persons assigned female sex at birth who have undergone gender-affirmation genital surgery is low. Providers should consider the anatomic diversity among transgender men because a person can undergo a metoidioplasty (a procedure to increase the length of the clitoris), with or without urethral lengthening, and might not have a hysterectomy and oophorectomy and therefore be at risk for bacterial STIs, HPV, HSV, HIV, and cervical cancer (366). For transgender men using gender-affirming hormone therapy, the decrease in estradiol levels caused by exogenous testosterone can lead to vaginal atrophy (367,368) and is associated with a high prevalence of unsatisfactory sample acquisition (369). The impact of these hormonal changes on mucosal susceptibility to HIV and STIs is unknown.

Transgender men who have not chosen to undergo hysterectomy with removal of the cervix remain at risk for cervical cancer. These persons often avoid cervical cancer screening because of multiple factors, including discomfort with medical examinations and fear of discrimination (338,370). Providers should be aware that conducting a speculum examination can be technically difficult after metoidioplasty surgery because of narrowing of the introitus. In these situations, high-risk HPV testing using a swab can be considered; self-collected swabs for high-risk HPV testing has been reported to be an acceptable option for transgender men (371).

## Screening Recommendations

The following are screening recommendations for transgender and gender diverse persons:

- Because of the diversity of transgender persons regarding surgical gender-affirming procedures, hormone use, and their patterns of sexual behavior, providers should remain aware of symptoms consistent with common STIs and screen for asymptomatic infections on the basis of the patient's sexual practices and anatomy.
- Gender-based screening recommendations should be adapted on the basis of anatomy (e.g., routine screening for *C. trachomatis* and *N. gonorrhoeae*) as recommended for all sexually active females aged <25 years on an annual basis and should be extended to transgender men and nonbinary persons with a cervix among this age group.

- HIV screening should be discussed and offered to all transgender persons. Frequency of repeat screenings should be based on level of risk.
- For transgender persons with HIV infection who have sex with cisgender men and transgender women, STI screening should be conducted at least annually, including syphilis serology, HCV testing, and urogenital and extragenital NAAT for gonorrhea and chlamydia.
- Transgender women who have had vaginoplasty surgery should undergo routine STI screening for all exposed sites (e.g., oral, anal, or vaginal). No data are available regarding the optimal screening method (urine or vaginal swab) for bacterial STIs of the neovagina. The usual techniques for creating a neovagina do not result in a cervix; therefore, no rationale exists for cervical cancer screening (368).
- If transgender men have undergone metoidioplasty surgery with urethral lengthening and have not had a vaginectomy, assessment of genital bacterial STIs should include a cervical swab because a urine specimen will be inadequate for detecting cervical infections.
- Cervical cancer screening for transgender men and nonbinary persons with a cervix should follow current screening guidelines (see Human Papillomavirus Infections).

## Persons in Correctional Facilities

Multiple studies have demonstrated that persons entering correctional facilities have a high prevalence of STIs, HIV, and viral hepatitis, especially those aged ≤35 years (141,372,373). Risk behaviors for acquiring STIs (e.g., having condomless sex, having multiple sex partners, substance misuse, and engaging in commercial, survival, or coerced sex) are common among incarcerated populations. Before their incarceration, many persons have had limited access to medical care. Other social determinants of health (e.g., insufficient social and economic support or living in communities with high local STI prevalence) are common. Addressing STIs in correctional settings is vital for addressing the overall STI impact among affected populations.

Growing evidence demonstrates the usefulness of expanded STI screening and treatment services in correctional settings, including short-term facilities (jails), long-term institutions (prisons), and juvenile detention centers. For example, in jurisdictions with comprehensive, targeted jail screening, more chlamydial infections among females (and males if screened) are detected and subsequently treated in the correctional setting than in any other single reporting source (141,374) and might represent the majority of reported cases in certain jurisdictions (375). Screening in the jail setting has the potential to reach

substantially more persons at risk than screening among the prison population alone.

Both males and females aged ≤35 years in juvenile and adult detention facilities have been reported to have higher rates of chlamydia and gonorrhea than nonincarcerated persons in the community (141,374,376). Syphilis seroprevalence rates, which can indicate previously treated or current infection, are considerably higher among incarcerated adult men and women than among adolescents, which is consistent with the overall national syphilis trends (141,374). Detection and treatment of early syphilis in correctional facilities might affect rates of transmission among adults and prevention of congenital syphilis (377).

In jails, approximately half of entrants are released back into the community within 48 hours. As a result, treatment completion rates for those screened for STIs and who receive STI diagnoses in short-term facilities might not be optimal. However, because of the mobility of incarcerated populations in and out of the community, the impact of screening in correctional facilities on the prevalence of infections among detainees and subsequent transmission in the community after release might be considerable (378). Moreover, treatment completion rates of ≥95% in short-term facilities can be achieved by offering screening at or shortly after intake, thus facilitating earlier receipt of test results and, if needed, follow-up of untreated persons can be conducted through public health outreach.

Universal, opt-out screening for chlamydia and gonorrhea among females aged ≤35 years entering juvenile and adult correctional facilities is recommended (379). Males aged <30 years entering juvenile and adult correctional facilities should also be screened for chlamydia and gonorrhea (380). Opt-out screening has the potential to substantially increase the number tested and the number of chlamydia and gonorrhea infections detected (381–385). Point-of-care (POC) NAAT might also be considered if the tests have demonstrated sufficient sensitivity and specificity. Studies have demonstrated high prevalence of trichomoniasis among incarcerated females (386–392).

## Screening Recommendations

### Chlamydia and Gonorrhea

Females aged ≤35 years and males aged <30 years housed in correctional facilities should be screened for chlamydia and gonorrhea. This screening should be conducted at intake and offered as opt-out screening.

### Trichomonas

Females aged ≤35 years housed in correctional facilities should be screened for trichomonas. This screening should be conducted at intake and offered as opt-out screening.

### Syphilis

Opt-out screening for incarcerated persons should be conducted on the basis of the local area and institutional prevalence of early (primary, secondary, or early latent) infectious syphilis. Correctional facilities should stay apprised of local syphilis prevalence. In short-term facilities, screening at entry might be indicated.

### Viral Hepatitis

All persons housed in juvenile and adult correctional facilities should be screened at entry for viral hepatitis, including HAV, HBV, and HCV, depending on local prevalence and the person's vaccination status. Vaccination for HAV and HBV should be offered if the person is susceptible.

### Cervical Cancer

Women and transgender men who are housed in correctional facilities should be screened for cervical cancer as for women who are not incarcerated (393,394) (see Cervical Cancer).

### HIV Infection

All persons being housed in juvenile and adult correctional facilities should be screened at entry for HIV infection; screening should be offered as opt-out screening. For those identified as being at risk for HIV infection (e.g., with diagnosed gonorrhea or syphilis or persons who inject drugs) and being released into the community, starting HIV PrEP (or providing linkage to a community clinic for HIV PrEP) for HIV prevention should be considered (395,396). Persons are likely to engage in high-risk activities immediately after release from incarceration (397). For those identified with HIV infection, treatment should be initiated. Those persons receiving PrEP or HIV treatment should have linkage to care established before release. Correctional settings should consider implementing other STI prevention approaches, both during incarceration and upon release, which might include educational and behavioral counseling interventions (398–401), vaccination (e.g., for HPV) (402,403), condom distribution (404,405), EPT (125), and PrEP to prevent HIV infection (see Primary Prevention Methods).

## HIV Infection

### Detection, Counseling, and Referral

Infection with HIV causes an acute but brief and nonspecific influenza-like retroviral syndrome that can include fever, malaise, lymphadenopathy, pharyngitis, arthritis, or skin rash. Most persons experience at least one symptom; however, some might be asymptomatic or have no recognition of illness (406–409). Acute infection transitions to a multiyear, chronic illness that progressively depletes CD4<sup>+</sup> T lymphocytes crucial for maintenance of effective immune function. Ultimately, persons with untreated HIV infection experience symptomatic, life-threatening immunodeficiency (i.e., AIDS).

Effective ART that suppresses HIV replication to undetectable levels reduces morbidity, provides a near-normal lifespan, and prevents sexual transmission of HIV to others (95–97,410–412). Early diagnosis of HIV and rapid linkage to care are essential for achieving these goals. Guidelines from both the U.S. Department of Health and Human Services and the International AIDS Society—USA Panel recommend that all persons with HIV infection be offered effective ART as soon as possible, both to reduce morbidity and mortality and to prevent HIV transmission (413).

STD specialty or sexual health clinics are a vital partner in reducing HIV infections in the United States. These clinics provide safety net services to vulnerable populations in need of HIV prevention services who are not served by the health care system and HIV partner service organizations. Diagnosis of an STI is a biomarker for HIV acquisition, especially among persons with primary or secondary syphilis or, among MSM, rectal gonorrhea or chlamydia (197). STD clinics perform only approximately 20% of all federally funded HIV tests nationally but identify approximately 30% of all new infections (414). Among testing venues, STD clinics are high performing in terms of linkage to HIV care within 90 days of diagnosis; during 2013–2017, the percentage of persons with a new diagnosis in an STD clinic and linked to care within 90 days increased from 55% to >90% (415,415).

### Screening Recommendations

The following recommendations apply to testing for HIV:

- HIV testing is recommended for all persons seeking STI evaluation who are not already known to have HIV infection. Testing should be routine at the time of the STI evaluation, regardless of whether the patient reports any specific behavioral risks for HIV. Testing for HIV should be performed at the time of STI diagnosis and treatment if not performed at the initial STI evaluation and screening (82,195,416).
- CDC and USPSTF recommend HIV screening at least once for all persons aged 15–65 years (417).
- Persons at higher risk for HIV acquisition, including sexually active gay, bisexual, and other MSM, should be screened for HIV at least annually. Providers can consider the benefits of offering more frequent screening (e.g., every 3–6 months) among MSM at increased risk for acquiring HIV (418,419).
- All pregnant women should be tested for HIV during the first prenatal visit. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered and is recommended for women who are at high risk for acquiring HIV infection, women who receive health care in jurisdictions with high rates of HIV, and women examined in clinical settings in which HIV incidence is ≥1 per 1,000 women screened per year (138,140).
- HIV screening should be voluntary and free from coercion. Patients should not be tested without their knowledge.
- Opt-out HIV screening (notifying the patient that an HIV test will be performed, unless the patient declines) is recommended in all health care settings. CDC also recommends that consent for HIV screening be incorporated into the general informed consent for medical care in the same manner as other screening or diagnostic tests.
- Requirement of specific signed consent for HIV testing is not recommended. General informed consent for medical care is considered sufficient to encompass informed consent for HIV testing.
- Providers should use a laboratory-based antigen/antibody (Ag/Ab) combination assay as the first test for HIV, unless persons are unlikely to follow up with a provider to receive their HIV test results; in those cases screening with a rapid POC test can be useful.
- Preliminary positive screening tests for HIV should be followed by supplemental testing to establish the diagnosis.
- Providing prevention counseling as part of HIV screening programs or in conjunction with HIV diagnostic testing is not required (6). However, persons might be more likely to think about HIV and consider their risk-related behavior when undergoing an HIV test. HIV testing gives providers an opportunity to conduct STI and HIV prevention counseling and communicate risk-reduction messages.
- Acute HIV infection can occur among persons who report recent sexual or needle-sharing behavior or who have had an STI diagnosis.
- Providers should test for HIV RNA if initial testing according to the HIV testing algorithm recommended by CDC is negative or indeterminate when concerned about acute HIV infection (<https://stacks.cdc.gov/view/cdc/50872>).

- Providers should not assume that a laboratory report of a negative HIV Ag/Ab or antibody test indicates that the requisite HIV RNA testing for acute HIV infection has been conducted. They should consider explicitly requesting HIV RNA testing when concerned about early acute HIV infection.
- Providers should assess eligibility of all persons seeking STI services for HIV PrEP and PEP. For persons with substantial risk whose results are HIV negative, providers should offer or provide referral for PrEP services, unless the last potential HIV exposure occurred <72 hours, in which case PEP might be indicated.

## Diagnostic Considerations

HIV infection can be diagnosed by HIV 1/2 Ag/Ab combination immunoassays. All FDA-cleared HIV tests are highly sensitive and specific. Available serologic tests can detect all known subtypes of HIV-1. The majority also detect HIV-2 and uncommon variants of HIV-1 (e.g., group O and group N).

According to an algorithm for HIV diagnosis, CDC recommends that HIV testing begin with a laboratory-based HIV-1/HIV-2 Ag/Ab combination assay, which, if repeatedly reactive, is followed by a laboratory-based assay with a supplemental HIV-1/HIV-2 antibody differentiation assay (<https://stacks.cdc.gov/view/cdc/50872>). This algorithm confers an additional advantage because it can detect HIV-2 antibodies after the initial immunoassay. Although HIV-2 is uncommon in the United States, accurate identification is vital because monitoring and therapy for HIV-2 differs from that for HIV-1 (420). RNA testing should be performed on all specimens with reactive immunoassay but negative supplemental antibody test results to determine whether the discordance represents acute HIV infection.

Rapid POC HIV tests can enable clinicians to make a preliminary diagnosis of HIV infection in <20 minutes. The majority of rapid antibody assays become reactive later in the course of HIV infection than conventional laboratory-based assays and thus can produce negative results among persons recently infected (e.g., acutely infected persons). Furthermore, HIV home-test kits only detect HIV antibodies and therefore will not detect acute HIV infection. If early or acute infection is suspected and a rapid HIV antibody assay is negative, confirmatory testing with combined laboratory-based assays or RNA testing should be performed. CDC recommends that all persons with reactive rapid tests be assessed with a laboratory-based Ag/Ab assay. Additional details about interpretation of results by using the HIV testing algorithm recommended by CDC are available at <https://stacks.cdc.gov/view/cdc/48472>.

## Acute HIV Infection

Providers serving persons at risk for STIs are in a position to diagnose HIV infection during its acute phase. Diagnosing HIV infection during the acute phase is particularly important because persons with acute HIV have highly infectious disease due to the concentration of virus in plasma and genital secretions, which is extremely elevated during that stage of infection (421,422) (<https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/acute-and-recent-early-hiv-infection?view=full>). ART during acute HIV infection is recommended because it substantially reduces infection transmission to others, improves laboratory markers of disease, might decrease severity of acute disease, lowers viral setpoint, reduces the size of the viral reservoir, decreases the rate of viral mutation by suppressing replication, and preserves immune function (<https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/acute-and-recent-early-hiv-infection?view=full>). Persons who receive an acute HIV diagnosis should be referred immediately to an HIV clinical care provider, provided prevention counseling (e.g., advised to reduce the number of partners and to use condoms correctly and consistently), and screened for STIs. Information should be provided regarding availability of PEP for sexual and injecting drug use partners not known to have HIV infection if the most recent contact was <72 hours preceding HIV diagnosis.

When providers test by using the CDC algorithm, specimens collected during acute infection might give indeterminate or negative results because insufficient anti-HIV antibodies and potentially insufficient antigen are present to be reactive on Ag/Ab combination assays and supplemental HIV-1/HIV-2 antibody differentiation assays. Whenever acute HIV infection is suspected (e.g., initial testing according to the CDC algorithm is negative or indeterminate after a possible sexual exposure to HIV within the previous few days to weeks, especially if the person has symptoms or has primary or secondary syphilis, gonorrhea, or chlamydia), additional testing for HIV RNA is recommended. If this additional testing for HIV RNA is also negative, repeat testing in a few weeks is recommended to rule out very early acute infection when HIV RNA might not be detectable. A more detailed discussion of testing in the context of acute HIV infection is available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/initiation-antiretroviral-therapy?view=full>.

## Treatment

ART should be initiated as soon as possible for all persons with HIV infection regardless of CD4<sup>+</sup> T-cell count, both for individual health and to prevent HIV transmission (<https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf>).

Persons with HIV infection who achieve and maintain a viral load suppressed to <200 copies/mL with ART have effectively no risk for sexually transmitting HIV (95–97,421). Early HIV diagnosis and treatment is thus not only vital for individual health but also as a public health intervention to prevent new infections. Knowledge of the prevention benefit of treatment can help reduce stigma and increase the person's commitment to start and remain adherent to ART (423). The importance of adherence should be stressed as well as the fact that ART does not protect against other STIs that can be prevented by using condoms. Interventions to assist persons to remain adherent to their prescribed HIV treatment, to otherwise reduce the possibility of transmission to others, and to protect themselves against STIs, have been developed for diverse populations at risk (424) (<https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf>).

Comprehensive HIV treatment and care services might not be available in facilities focused primarily on STI treatment. Providers in such settings should be knowledgeable about HIV treatment and care options available in their communities and promptly link persons who have newly diagnosed HIV infection and any persons with HIV infection who are not engaged in ongoing effective care to a health care provider or facility experienced in caring for persons living with HIV (<https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf>).

### Other HIV Management Considerations

Behavioral and psychosocial services are integral to caring for persons with HIV infection. Providers should expect persons to be distressed when first informed that they have HIV. They face multiple adaptive challenges, including coping with the reactions of others to a stigmatizing illness, developing and adopting strategies to maintain physical and emotional health, initiating changes in behavior to prevent HIV transmission to others, and reducing the risk for acquiring additional STIs. Many persons will require assistance gaining access to health care and other support services and coping with changes in personal relationships.

Persons with HIV infection might have additional needs (e.g., referral for substance use or mental health disorders). Others require assistance to secure and maintain employment and housing. Persons capable of reproduction might require family planning counseling, information about reproductive health choices, and referral for reproductive health care.

The following recommendations apply to managing persons with diagnosed HIV infection:

- Link persons with HIV infection to care and start them on ART as soon as possible.
- Report cases (in accordance with local requirements) to public health and initiate partner services.

- Provide prevention counseling to persons with diagnosed HIV infection.
- Ensure all persons with HIV infection are informed that if they achieve and maintain a suppressed viral load, they have effectively no risk for transmitting HIV. Stress that a suppressed viral load is not a substitute for condoms and behavioral modifications because ART does not protect persons with HIV against other STIs.
- Provide additional counseling, either on-site or through referral, about the psychosocial and medical implications of having HIV infection.
- Assess the need for immediate medical care and psychosocial support.
- Link persons with diagnosed HIV infection to services provided by health care personnel experienced in managing HIV infection. Additional services that might be needed include substance misuse counseling and treatment, treatment for mental health disorders or emotional distress, reproductive counseling, risk-reduction counseling, and case management. Providers should follow up to ensure that patients have received services for any identified needs.
- Persons with HIV infection should be educated about the importance of ongoing medical care and what to expect from these services.

### STI Screening of Persons with HIV Infection in HIV Care Settings

At the initial HIV care visit, providers should screen all sexually active persons for syphilis, gonorrhea, and chlamydia, and perform screening for these infections at least annually during the course of HIV care (425). Specific testing includes syphilis serology and NAAT for *N. gonorrhoeae* and *C. trachomatis* at the anatomic site of exposure. Women should also be screened for trichomoniasis at the initial visit and annually thereafter. Women should be screened for cervical cancer precursor lesions per existing guidelines (98).

More frequent screening for syphilis, gonorrhea, and chlamydia (e.g., every 3 or 6 months) should be tailored to individual risk and the local prevalence of specific STIs. Certain STIs can be asymptomatic; their diagnosis might prompt referral for partner services, might identify sexual and needle-sharing partners who can benefit from early diagnosis and treatment of HIV, and might prompt reengagement in care or HIV prevention services (e.g., PEP or PrEP) (8). More detailed information on screening, testing, and treatment is provided in pathogen-specific sections of this report.

## Partner Services and Reporting

Partner notification is a key component in the evaluation of persons with HIV infection. Early diagnosis and treatment of HIV among all potentially exposed sexual and injecting drug sharing partners can improve their health and reduce new infections. For those partners without HIV infection, partner services also provide an opportunity for offering HIV prevention services, including PrEP or PEP (if exposure was <72 hours previous) and STI testing and treatment.

Health care providers should inform persons with diagnosed HIV infection about any legal obligations of providers to report cases of HIV to public health; the local confidential processes for managing partner services, including that a public health department still might be in contact to follow up in their care and partner services; and the benefits and risks of partner notification and services. Health care providers should also encourage persons with a new HIV diagnosis to notify their partners and provide them with referral information for their partners about HIV testing. Partner notification for exposure to HIV should be confidential. Health care providers can assist in the partner notification process, either directly or by referral to health department partner notification programs. Health department staff are trained to use public health investigation strategies for confidentially locating persons who can benefit from HIV treatment, care, or prevention services. Guidance regarding spousal notification varies by jurisdiction. Detailed recommendations for notification, evaluation, and treatment of exposed partners are available in *Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infections* (111).

## Special Considerations

### Pregnancy

All pregnant women should be tested for HIV during the first prenatal visit. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered and is recommended for women who are at high risk for acquiring HIV, women who receive health care in jurisdictions with high rates of HIV infection, and women served in clinical settings in which prenatal screening identifies ≥1 pregnant woman with HIV per 1,000 women screened (138). Diagnostic algorithms for HIV for pregnant women do not differ from those for nonpregnant women (see STI Detection Among Special Populations). Pregnant women should be informed that HIV testing will be performed as part of the routine panel of prenatal tests (138); for women who decline HIV testing, providers should address concerns that pose obstacles, discuss the benefits of testing (e.g., early HIV detection, treatment, and care for improving health of the mother and reducing perinatal

transmission of HIV), and encourage testing at subsequent prenatal visits. Women who decline testing because they have had a previous negative HIV test result should be informed about the importance of retesting during each pregnancy. Women with no prenatal care should be tested for HIV at the time of delivery.

Testing pregnant women is crucial because knowledge of infection status can help maintain the woman's health, and it enables receipt of interventions (i.e., ART or specialized obstetrical care) that can substantially reduce the risk for perinatal transmission of HIV. Pregnant women with diagnosed HIV infection should be educated about the benefits of ART for their own health and for reducing the risk for HIV transmission to their infant. In the absence of ART, a mother's risk for transmitting HIV to her neonate is approximately 30%; however, risk can be reduced to <2% through ART, obstetrical interventions (i.e., elective cesarean delivery at 38 weeks' pregnancy), and breastfeeding avoidance (<https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf>). Pregnant women with HIV infection should be linked to an HIV care provider experienced in managing HIV in pregnancy and provided antenatal and postpartum treatment and advice. Detailed and regularly updated recommendations for managing pregnant patients with HIV infection are available at <https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf>.

### HIV Infection Among Neonates, Infants, and Children

Diagnosis of HIV infection in a pregnant woman indicates the need for evaluating and managing the HIV-exposed neonate and considering whether the woman's other children, if any, might be infected. Detailed recommendations regarding diagnosis and management of HIV infection among neonates and children of mothers with HIV are beyond the scope of these guidelines but are available at <https://clinicalinfo.hiv.gov/en/guidelines>. Exposed neonates and children with HIV infection should be referred to physicians with expertise in neonatal and pediatric HIV management.

## Diseases Characterized by Genital, Anal, or Perianal Ulcers

In the United States, the majority of young, sexually active patients who have genital, anal, or perianal ulcers have either genital herpes or syphilis. The frequency of each condition differs by geographic area and population; however, genital herpes is the most prevalent of these diseases. More than one etiologic agent (e.g., herpes and syphilis) can be present in any genital, anal, or perianal ulcer. Less common infectious

causes of genital, anal, or perianal ulcers include chancroid, LGV, and granuloma inguinale (donovanosis). GUDs (e.g., syphilis, herpes, and LGV) might also present as oral ulcers. Genital herpes, syphilis, chlamydia, gonorrhea, and chancroid have been associated with an increased risk for HIV acquisition and transmission. Genital, anal, or perianal lesions can also be associated with infectious and noninfectious conditions that are not sexually transmitted (e.g., yeast, trauma, carcinoma, aphthae or Behcet's disease, fixed drug eruption, or psoriasis).

A diagnosis based only on medical history and physical examination frequently can be inaccurate. Therefore, all persons who have genital, anal, or perianal ulcers should be evaluated. Specific evaluation of genital, anal, or perianal ulcers includes syphilis serology tests and darkfield examination from lesion exudate or tissue, or NAAT if available; NAAT or culture for genital herpes type 1 or 2; and serologic testing for type-specific HSV antibody. In settings where chancroid is prevalent, a NAAT or culture for *Haemophilus ducreyi* should be performed.

No FDA-cleared NAAT for diagnosing syphilis is available in the United States; however, multiple FDA-cleared NAATs are available for diagnosing HSV-1 and HSV-2 in genital specimens. Certain clinical laboratories have developed their own syphilis and HSV NAATs and have conducted Clinical Laboratory Improvement Amendment (CLIA) verification studies with genital specimens. Type-specific serology for HSV-2 might aid in identifying persons with genital herpes (see Genital Herpes). In addition, biopsy of ulcers with immunohistochemistry can help identify the cause of ulcers that are unusual or that do not respond to initial therapy. HIV testing should be performed on all persons not known to have HIV infection who present with genital, anal, or perianal ulcers (see Diagnostic Considerations in disease-specific sections). NAAT testing at extragenital sites should be considered for cases in which GUDs are suspected (e.g., oral manifestations of syphilis, herpes, or LGV). Commercially available NAATs have not been cleared by FDA for these indications; however, they can be used by laboratories that have met regulatory requirements for an off-label procedure.

Because early syphilis treatment decreases transmission possibility, public health standards require health care providers to presumptively treat any patient with a suspected case of infectious syphilis at the initial visit, even before test results are available. Presumptive treatment of a patient with a suspected first episode of genital herpes also is recommended because HSV treatment benefits depend on prompt therapy initiation. The clinician should choose the presumptive treatment on the basis of the clinical presentation (i.e., HSV lesions begin as vesicles and primary syphilis as a papule) and epidemiologic circumstances (e.g., high incidence of disease

among populations and communities and travel history). For example, syphilis is so common among MSM that any male who has sex with men presenting with a genital ulcer should be presumptively treated for syphilis at the initial visit after syphilis and HSV tests are performed. After a complete diagnostic evaluation, >25% of patients who have genital ulcers might not have a laboratory-confirmed diagnosis (426).

## Chancroid

Chancroid prevalence has declined in the United States (141). When infection does occur, it is usually associated with sporadic outbreaks. Worldwide, chancroid appears to have decreased as well, although infection might still occur in certain Africa regions and the Caribbean. Chancroid is a risk factor in HIV transmission and acquisition (197).

## Diagnostic Considerations

A definitive diagnosis of chancroid requires identifying *H. ducreyi* on special culture media that is not widely available from commercial sources; even when these media are used, sensitivity is <80% (427). No FDA-cleared NAAT for *H. ducreyi* is available in the United States; however, such testing can be performed by clinical laboratories that have developed their own NAAT and have conducted CLIA verification studies on genital specimens.

The combination of one or more deep and painful genital ulcers and tender suppurative inguinal adenopathy indicates the chancroid diagnosis; inguinal lymphadenitis typically occurs in <50% of cases (428). For both clinical and surveillance purposes, a probable diagnosis of chancroid can be made if all of the following four criteria are met: 1) the patient has one or more painful genital ulcers; 2) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; 3) the patient has no evidence of *T. pallidum* infection by darkfield examination or NAAT (i.e., ulcer exudate or serous fluid) or by serologic tests for syphilis performed at least 7–14 days after onset of ulcers; and 4) HSV-1 or HSV-2 NAAT or HSV culture performed on the ulcer exudate or fluid are negative.

## Treatment

Successful antimicrobial treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. In advanced cases, genital scarring and rectal or urogenital fistulas from suppurative buboes can result despite successful therapy.

**Recommended Regimens for Chancroid**

Azithromycin 1 g orally in a single dose  
*or*  
 Ceftriaxone 250 mg IM in a single dose  
*or*  
 Ciprofloxacin 500 mg orally 2 times/day for 3 days  
*or*  
 Erythromycin base 500 mg orally 3 times/day for 7 days

Azithromycin and ceftriaxone offer the advantage of single-dose therapy (429). Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported. However, because cultures are not routinely performed, and chancroid is uncommon, data are limited regarding prevalence of *H. ducreyi* antimicrobial resistance.

**Other Management Considerations**

Men who are uncircumcised and persons with HIV infection do not respond as well to treatment as persons who are circumcised or are HIV negative (430). Patients should be tested for HIV at the time chancroid is diagnosed. If the initial HIV test results were negative, the provider can consider the benefits of offering more frequent testing and HIV PrEP to persons at increased risk for HIV infection.

**Follow-Up**

Patients should be reexamined 3–7 days after therapy initiation. If treatment is successful, ulcers usually improve symptomatically within 3 days and objectively within 7 days after therapy. If no clinical improvement is evident, the clinician should consider whether the diagnosis is correct, another STI is present, the patient has HIV infection, the treatment was not used as instructed, or the *H. ducreyi* strain causing the infection is resistant to the prescribed antimicrobial. The time required for complete healing depends on the size of the ulcer; large ulcers might require >2 weeks. In addition, healing can be slower for uncircumcised men who have ulcers under the foreskin. Clinical resolution of fluctuant lymphadenopathy is slower than that of ulcers and might require needle aspiration or incision and drainage, despite otherwise successful therapy. Although needle aspiration of buboes is a simpler procedure, incision and drainage might be preferred because of reduced need for subsequent drainage procedures.

**Management of Sex Partners**

Regardless of whether disease symptoms are present, sex partners of patients with chancroid should be examined and treated if they had sexual contact with the patient during the 10 days preceding the patient's symptom onset.

**Special Considerations****Pregnancy**

Data indicate ciprofloxacin presents a low risk to the fetus during pregnancy but has potential for toxicity during breastfeeding (431). Alternative drugs should be used if the patient is pregnant or lactating. No adverse effects of chancroid on pregnancy outcome have been reported.

**HIV Infection**

Persons with HIV infection who have chancroid infection should be monitored closely because they are more likely to experience chancroid treatment failure and to have ulcers that heal slowly (430,432). Persons with HIV might require repeated or longer courses of therapy, and treatment failures can occur with any regimen. Data are limited concerning the therapeutic efficacy of the recommended single-dose azithromycin and ceftriaxone regimens among persons with HIV infection.

**Children**

Because sexual contact is the major primary transmission route among U.S. patients, diagnosis of chancroid ulcers among infants and children, especially in the genital or perineal region, is highly suspicious of sexual abuse. However, *H. ducreyi* is recognized as a major cause of nonsexually transmitted cutaneous ulcers among children in tropical regions and, specifically, countries where yaws is endemic (433–435). Acquisition of a lower-extremity ulcer attributable to *H. ducreyi* in a child without genital ulcers and reported travel to a region where yaws is endemic should not be considered evidence of sexual abuse.

**Genital Herpes**

Genital herpes is a chronic, lifelong viral infection. Two types of HSV can cause genital herpes: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2, and 11.9% of persons aged 14–49 years are estimated to be infected in the United States (436). However, an increasing proportion of anogenital herpetic infections have been attributed to HSV-1, which is especially prominent among young women and MSM (186,437,438).

The majority of persons infected with HSV-2 have not had the condition diagnosed, many of whom have mild or unrecognized infections but shed virus intermittently in the anogenital area. Consequently, most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. Management of genital HSV should address the chronic nature of the infection rather than focusing solely on treating acute episodes of genital lesions.

## Diagnostic Considerations

Clinical diagnosis of genital herpes can be difficult because the self-limited, recurrent, painful, and vesicular or ulcerative lesions classically associated with HSV are absent in many infected persons at the time of clinical evaluation. If genital lesions are present, clinical diagnosis of genital herpes should be confirmed by type-specific virologic testing from the lesion by NAAT or culture (186). Recurrences and subclinical shedding are much more frequent for HSV-2 genital herpes infection than for HSV-1 genital herpes (439,440). Therefore, prognosis and counseling depend on which HSV type is present. Type-specific serologic tests can be used to aid in the diagnosis of HSV infection in the absence of genital lesions. Both type-specific virologic and type-specific serologic tests for HSV should be available in clinical settings that provide care to persons with or at risk for STIs. HSV-2 genital herpes infection increases the risk for acquiring HIV twofold to threefold; therefore, all persons with genital herpes should be tested for HIV (441).

### Virologic Tests

HSV NAAT assays are the most sensitive tests because they detect HSV from genital ulcers or other mucocutaneous lesions; these tests are increasingly available (442–444). Although multiple FDA-cleared assays exist for HSV detection, these tests vary in sensitivity from 90.9% to 100%; however, they are considered highly specific (445–447). PCR is also the test of choice for diagnosing HSV infections affecting the central nervous system (CNS) and systemic infections (e.g., meningitis, encephalitis, and neonatal herpes). HSV PCR of the blood should not be performed to diagnose genital herpes infection, except in cases in which concern exists for disseminated infection (e.g., hepatitis). In certain settings, viral culture is the only available virologic test. The sensitivity of viral culture is low, especially for recurrent lesions, and decreases rapidly as lesions begin to heal (443,448). Viral culture isolates and PCR amplicons should be typed to determine whether HSV-1 or HSV-2 is causing the infection. Failure to detect HSV by NAAT or culture, especially in the presence of older lesions or the absence of active lesions, does not indicate an absence of HSV infection because viral shedding is intermittent. Similarly, random or blind genital swabs in the absence of lesions should not be used to diagnose genital HSV infection because sensitivity is low, and a negative result does not exclude the presence of HSV infection.

Cytologic detection of cellular changes associated with HSV infection is an insensitive and nonspecific method of diagnosing genital lesions (i.e., Tzanck preparation) and therefore should not be relied on. Although a direct immunofluorescence assay using fluorescein-labeled monoclonal antibodies is also available for detecting HSV antigen from genital specimens, this assay lacks sensitivity and is not recommended (449).

### Type-Specific Serologic Tests

Both type-specific and type-common antibodies to HSV develop during the first weeks after infection and persist indefinitely. The majority of available, accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (gG2) (HSV-2) and glycoprotein G1 (gG1) (HSV-1). Type-common antibody tests do not distinguish between HSV-1 and HSV-2 infection; therefore, type-specific serologic assays should be requested (450–452).

Both laboratory-based assays and POC tests that provide results for HSV-2 antibodies from capillary blood or serum during a clinic visit are available. The sensitivity of glycoprotein G type-specific tests for detecting HSV-2 antibody varies from 80% to 98%; false-negative results might be more frequent at early stages of infection (451,453,454). Therefore, in cases of recent suspected HSV-2 acquisition, repeat type-specific antibody testing 12 weeks after the presumed time of acquisition is indicated. The most commonly used test, HerpeSelect HSV-2 enzyme immunoassay (EIA), often is falsely positive at low index values (1.1–3.0) (457–457). One study reported an overall specificity of 57.4%, with a specificity of 39.8% for index values of 1.1–2.9 (458). Because of the poor specificity of commercially available type-specific EIAs, particularly with low index values (<3.0), a confirmatory test (Biokit or Western blot) with a second method should be performed before test interpretation. Use of confirmatory testing with the Biokit or the Western blot assays have been reported to improve accuracy of HSV-2 serologic testing (459). The HerpeSelect HSV-2 immunoblot should not be used for confirmation because it uses the same antigen as the HSV-2 EIA. If confirmatory tests are unavailable, patients should be counseled about the limitations of available testing before obtaining serologic tests, and health care providers should be aware that false-positive results occur. Immunoglobulin M (IgM) testing for HSV-1 or HSV-2 is not useful because IgM tests are not type specific and might be positive during recurrent genital or oral episodes of herpes (460). Therefore, HSV IgM testing is not recommended.

Because approximately all HSV-2 infections are sexually acquired, presence of type-specific HSV-2 antibody implies anogenital infection. In this instance, education and counseling for persons with genital HSV infections should be provided. The presence of HSV-1 antibody alone is more difficult to interpret. HSV-1 serologic testing does not distinguish between oral and genital infection and typically should not be performed for diagnosing genital HSV-1 infection. Persons with HSV-1 antibodies often have oral HSV infection acquired during childhood, which might be asymptomatic. Lack of symptoms in a person who is HSV-1 seropositive does not

distinguish anogenital from orolabial or cutaneous infection, and, regardless of site of infection, these persons remain at risk for acquiring HSV-2. In addition, HSV-1 serologic testing has low sensitivity for detection of HSV-1 antibody (458). However, acquisition of HSV-1 genital herpes is increasing, and HSV-1 genital herpes also can be asymptomatic (437–439,461,462). Diagnosis of HSV-1 infection is confirmed by virologic tests from genital lesions.

Type-specific HSV-2 serologic assays for diagnosing HSV-2 are useful in the following scenarios: recurrent or atypical genital symptoms or lesions with a negative HSV PCR or culture result, clinical diagnosis of genital herpes without laboratory confirmation, and a patient's partner has genital herpes. HSV-2 serologic screening among the general population is not recommended. Patients who are at higher risk for infection (e.g., those presenting for an STI evaluation, especially for persons with ≥10 lifetime sex partners, and persons with HIV infection) might need to be assessed for a history of genital herpes symptoms, followed by type-specific HSV serologic assays to diagnose genital herpes for those with genital symptoms.

## Genital Herpes Management

Antiviral medication offers clinical benefits to symptomatic patients and is the mainstay of management. The goals for use of antiviral medications to treat genital herpes infection are to treat or prevent symptomatic genital herpes recurrences and improve quality of life and suppress the virus to prevent transmission to sexual partners. Counseling regarding the natural history of genital herpes, risks for sexual and perinatal transmission, and methods for reducing transmission is also integral to clinical management.

Systemic antiviral drugs can partially control the signs and symptoms of genital herpes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. Randomized trials have indicated that three FDA-approved antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir (463–471). Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration, allowing for less frequent dosing than acyclovir. Famciclovir also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit and is discouraged.

## First Clinical Episode of Genital Herpes

Newly acquired genital herpes can cause a prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even persons with first-episode herpes who have

mild clinical manifestations initially can experience severe or prolonged symptoms during recurrent infection. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy.

### Recommended Regimens for First Clinical Episode of Genital Herpes\*

**Acyclovir<sup>†</sup>** 400 mg orally 3 times/day for 7–10 days  
or  
**Famciclovir** 250 mg orally 3 times/day for 7–10 days  
or  
**Valacyclovir** 1 g orally 2 times/day for 7–10 days

\* Treatment can be extended if healing is incomplete after 10 days of therapy.

<sup>†</sup> Acyclovir 200 mg orally 5 times/day is also effective but is not recommended because of the frequency of dosing.

## Recurrent HSV-2 Genital Herpes

Almost all persons with symptomatic first-episode HSV-2 genital herpes subsequently experience recurrent episodes of genital lesions. Intermittent asymptomatic shedding occurs among persons with HSV-2 genital herpes infection, even those with longstanding clinically silent infection. Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Certain persons, including those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy; therefore, options for treatment should be discussed. Many persons prefer suppressive therapy, which has the additional advantage of decreasing the risk for transmitting HSV-2 genital herpes to susceptible partners (472,473).

## Suppressive Therapy for Recurrent HSV-2 Genital Herpes

Suppressive therapy reduces frequency of genital herpes recurrences by 70%–80% among patients who have frequent recurrences (469–472). Persons receiving such therapy often report having experienced no symptomatic outbreaks. Suppressive therapy also is effective for patients with less frequent recurrences. Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir (474). Quality of life is improved for many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment (475). Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. However, neither treatment discontinuation nor laboratory monitoring is necessary because adverse events and development of HSV antiviral resistance related to long-term antiviral use are uncommon.

Treatment with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission for discordant heterosexual couples in which a partner has a history of genital HSV-2 infection (473). Such couples should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. HSV-2 seropositive persons without a history of symptomatic genital herpes have a 50% decreased risk for genital shedding, compared with those with symptomatic genital herpes (476). No data are available regarding efficacy of suppressive therapy for preventing HSV-2 transmission among discordant couples in which a partner has a history of asymptomatic HSV-2 infection identified by a positive HSV-2 serologic test. Among HSV-2 seropositive persons without HIV infection, oral TDF/FTC and intravaginal tenofovir are ineffective at reducing the risk for HSV-2 shedding or recurrences (477).

#### Recommended Regimens for Suppression of Recurrent HSV-2 Genital Herpes

**Acyclovir** 400 mg orally 2 times/day

or

**Valacyclovir** 500 mg orally once a day\*

or

**Valacyclovir** 1 g orally once a day

or

**Famciclovir** 250 mg orally 2 times/day

\* Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e.,  $\geq 10$  episodes/year).

prodrome that precedes some outbreaks. The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes (466–470).

#### Recommended Regimens for Episodic Therapy for Recurrent HSV-2 Genital Herpes\*

**Acyclovir** 800 mg orally 2 times/day for 5 days  
or  
**Acyclovir** 800 mg orally 3 times/day for 2 days

or  
**Famciclovir** 1 g orally 2 times/day for 1 day  
or

**Famciclovir** 500 mg orally once, followed by 250 mg 2 times/day for 2 days  
or

**Famciclovir** 125 mg orally 2 times/day for 5 days  
or

**Valacyclovir** 500 mg orally 2 times/day for 3 days  
or

**Valacyclovir** 1 g orally once daily for 5 days

\* Acyclovir 400 mg orally 3 times/day for 5 days is also effective but is not recommended because of frequency of dosing.

#### Severe Disease

Intravenous (IV) acyclovir therapy (5–10 mg/kg body weight IV every 8 hours) should be provided for patients who have severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningitis or encephalitis). HSV-2 meningitis is a rare complication of HSV-2 genital herpes infection that affects women more than men (480). IV therapy should be considered until clinical improvement followed by oral antiviral therapy to complete >10 days of total therapy. Longer duration is recommended for CNS complications. HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose (481). Optimal therapies for HSV-2 meningitis have not been well studied (482); however, acyclovir 5–10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. For patients with previous episodes of documented HSV-2 meningitis, oral valacyclovir may be used for the entire course during episodes of recurrent HSV-2 meningitis. A randomized clinical trial indicated that suppressive therapy (valacyclovir 500 mg 2 times/day) did not prevent recurrent HSV-2 meningitis episodes; however, the dose might not have been sufficient for CNS penetration (483). Valacyclovir

Famciclovir appears somewhat less effective for suppression of viral shedding (478). Ease of administration and cost also are key considerations for prolonged treatment.

#### Recurrent HSV-1 Genital Herpes

Recurrences are less frequent after the first episode of HSV-1 genital herpes, compared with genital HSV-2 genital herpes, and genital shedding rapidly decreases during the first year of infection (479). No data are available regarding the efficacy of suppressive therapy for preventing transmission among persons with HSV-1 genital herpes infection. Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider.

#### Episodic Therapy for Recurrent HSV-2 Genital Herpes

Episodic treatment of recurrent herpes is most effective if therapy is initiated within 1 day of lesion onset or during the

500 mg 2 times/day is not recommended for suppression of HSV-2 meningitis; higher doses have not been studied in clinical trials. HSV meningitis should be distinguished from encephalitis, which requires a longer course (14–21 days) of IV therapy. Impaired renal function warrants an adjustment in acyclovir dosage.

## Hepatitis

Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy (484). Pregnant women in any trimester can present with fever and hepatitis (markedly elevated transaminases) but might not have any genital or skin lesions. HSV hepatitis is associated with fulminant liver failure and high mortality (25%). Therefore, a high index of suspicion for HSV is necessary, with a confirmatory diagnosis by HSV PCR from blood (485). Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation (484).

## Prevention

Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women (486–488). Condoms are less effective for preventing transmission from women to men (489). Two randomized clinical trials of medical male circumcision (MMC) demonstrated a decreased risk for HSV-2 acquisition among men in Uganda and South Africa (66,68). Results from a third trial conducted in Kenya did not demonstrate a substantial difference in HSV-2 acquisition among men who received MMC (490). A systematic review indicated high consistency for decreased risk for HSV-2 acquisition among women with a male partner who underwent MMC (491). These data indicate that MMC can be associated with decreased risk for HSV-2 acquisition among adult heterosexual men and with decreased risk for HSV-2 transmission from male to female partners.

Randomized clinical trials have demonstrated that PrEP with daily oral TDF/FTC decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships (492). Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women (493). Among MSM and transgender women, daily oral TDF/FTC decreases the risk for severe ulcers with symptomatic genital HSV-2 infection but not for HSV-2 acquisition (494). Insufficient evidence exists that TDF/FTC use among those who are not at risk for HIV acquisition will prevent HSV-2 infection, and it should not be used for that sole purpose. Oral TDF does not prevent HSV-2 acquisition among persons with HIV infection who

are taking TDF as part of their ART regimen (495). No data indicate that antivirals (acyclovir, valacyclovir, or famciclovir) can be taken as PrEP by persons without HSV-2 to prevent its acquisition.

## Counseling

Counseling of persons with genital herpes and their sex partners is crucial for management. The goals of counseling include helping patients cope with the infection and preventing sexual and perinatal transmission. Although initial counseling can be provided at the first visit, patients often benefit from learning about the chronic aspects of the disease after the acute illness subsides. Multiple resources, including Internet sites and printed materials, are available to assist patients, their partners, and clinicians who provide counseling (496,497) (<https://www.ashasexualhealth.org> and <https://www.cdc.gov/std/herpes>).

Although the psychological effect of a serologic diagnosis of HSV-2 infection in a person with asymptomatic or unrecognized genital herpes appears minimal and transient (498,499), certain persons with HSV infection might express anxiety concerning genital herpes that does not reflect the actual clinical severity of their disease; the psychological effect of HSV infection can be substantial. Common concerns about genital herpes include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children.

## Symptomatic HSV-2 Genital Herpes

When counseling persons with symptomatic HSV-2 genital herpes infection, the provider should discuss the following:

- The natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and the attendant risks for sexual transmission of HSV to occur during asymptomatic periods (asymptomatic viral shedding is most frequent during the first 12 months after acquiring HSV-2).
- The effectiveness of daily suppressive antiviral therapy for preventing symptomatic recurrent episodes of genital herpes for persons experiencing a first episode or recurrent genital herpes.
- The effectiveness of daily use of valacyclovir in reducing risk for transmission of HSV-2 among persons without HIV (473) and use of episodic therapy to shorten the duration of recurrent episodes.
- The importance of informing current sex partners about genital herpes and informing future partners before initiating a sexual relationship.
- The importance of abstaining from sexual activity with uninfected partners when lesions or prodromal symptoms are present.

- The effectiveness of male latex condoms, which when used consistently and correctly can reduce, but not eliminate, the risk for genital herpes transmission (486–488).
- The type-specific serologic testing of partners of persons with symptomatic HSV-2 genital herpes to determine whether such partners are already HSV seropositive or whether risk for acquiring HSV exists.
- The low risk for neonatal HSV except when genital herpes is acquired late in pregnancy or if prodrome or lesions are present at delivery.
- The increased risk for HIV acquisition among HSV-2 seropositive persons who are exposed to HIV (76,471).
- The lack of effectiveness of episodic or suppressive therapy among persons with HIV infection to reduce risk for transmission to partners who might be at risk for HSV-2 acquisition.

### **Asymptomatic HSV-2 Genital Herpes**

When counseling persons with asymptomatic HSV-2 genital herpes infection, the provider should consider the following:

- Asymptomatic persons who receive a diagnosis of HSV-2 by type-specific serologic testing (with confirmatory testing, if needed) should receive education about the symptoms of genital herpes infection (see Diagnostic Considerations).
- Episodic and suppressive antiviral therapies are used predominantly to treat recurrences, prevent recurrences, and prevent transmission to sex partners of persons with symptomatic HSV-2 infection.
- For patients with serological evidence of HSV-2 (with combination testing if needed) without symptomatic recurrences, neither episodic nor suppressive therapy is indicated for prevention of recurrences (see Diagnostic Considerations).
- Among persons with asymptomatic infection, the efficacy of suppressive therapy to prevent HSV-2 transmission to sex partners has not been studied.
- Because of the decreased risk for shedding among those with asymptomatic HSV-2 genital herpes, the benefit of suppressive therapy for preventing transmission is unknown among this population.

### **HSV-1 Genital Herpes**

When counseling persons with HSV-1 genital herpes infection, the provider should consider the following:

- Persons with virologic laboratory-documented symptomatic HSV-1 genital herpes infection should be educated that the risk for recurrent genital herpes and genital shedding is lower with HSV-1 infection, compared with HSV-2 infection.

- Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences.
- For patients with frequently recurring HSV-1 genital herpes, suppressive therapy might be considered. Suppressive therapy to prevent HSV-1 transmission to sex partners has not been studied.

For persons with symptomatic HSV-1 genital herpes or asymptomatic HSV-2 genital herpes, suppressive therapy can be considered for those who have substantial psychosocial distress caused by the diagnosis of genital herpes. For women who have genital herpes, the providers who care for them during pregnancy and those who will care for their newborn infant should be informed of their infection (see Genital Herpes During Pregnancy).

### **Management of Sex Partners**

The sex partners of persons who have symptomatic genital herpes can benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have symptomatic genital herpes. Asymptomatic sex partners of patients who have symptomatic genital herpes should be asked about a history of genital symptoms and offered type-specific serologic testing for HSV-2. For partners without genital herpes, no data are available on which to base a recommendation for PEP or PrEP with antiviral medications or that they would prevent acquisition, and this should not be offered to patients as a prevention strategy.

### **Special Considerations**

#### **Drug Allergy, Intolerance, or Adverse Reactions**

Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described (500).

#### **HIV Infection**

Immunocompromised patients can have prolonged or severe episodes of genital, perianal, or oral herpes. Lesions caused by HSV are common among persons with HIV infection and might be severe, painful, and atypical (501). HSV shedding is increased among persons with HIV infection (502). Whereas ART reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs (503,504). Clinical manifestations of genital herpes might worsen during immune reconstitution early after initiation of ART. HSV-2 type-specific serologic testing can be considered for persons with HIV infection during their initial evaluation, particularly among those with a history of genital symptoms indicative of HSV infection.

Recommended therapy for first-episode genital herpes is the same as for persons without HIV infection, although treatment courses might need to be extended for lesion resolution. Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV (503,504). The risk for GUD increases during the first 6 months after starting ART, especially among persons who have a CD4<sup>+</sup> T-cell count <200 cell/mm<sup>3</sup>. Suppressive antiviral therapy reduces the risk for GUD among this population and can be continued for 6 months after ART initiation (504) when the risk for GUD returns to baseline levels. Suppressive antiviral therapy among persons with HIV and HSV infection does not reduce the risk for either HIV transmission or HSV-2 transmission to susceptible sex partners (88,505). Suppressive antiviral therapy does not delay HIV disease progression and is not associated with decreased risk for HIV-related inflammation among persons taking ART (506). For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.

#### **Recommended Regimens for Daily Suppression of Genital Herpes Among Persons with HIV Infection**

Acyclovir 400–800 mg orally 2–3 times/day  
or  
Famciclovir 500 mg orally 2 times/day  
or  
Valacyclovir 500 mg orally 2 times/day

#### **Recommended Regimens for Episodic Genital Herpes Infection Among Persons with HIV Infection**

Acyclovir 400 mg orally 3 times/day for 5–10 days  
or  
Famciclovir 500 mg orally 2 times/day for 5–10 days  
or  
Valacyclovir 1 g orally 2 times/day for 5–10 days

#### **Antiviral-Resistant HSV Infection**

If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected and a viral culture obtained for phenotypic sensitivity testing (507). Molecular testing for acyclovir resistance is not available. Such persons should be managed in consultation with an infectious disease specialist, and alternative therapy should be administered. All acyclovir-resistant strains are also resistant to valacyclovir, and the majority are resistant to famciclovir. Foscarnet (40–80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes (508,509). Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. Foscarnet and cidofovir are nephrotoxic medications that require intensive laboratory monitoring and infectious

disease specialist consultation. Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective (510,511). Topical cidofovir gel 1% can be applied to lesions 2–4 times daily; however, cidofovir must be compounded at a pharmacy (512).

Prevention of antiviral resistance remains challenging among persons with HIV infection. Experience with another group of immunocompromised persons (e.g., hematopoietic stem-cell recipients) demonstrated that persons receiving daily suppressive antiviral therapy were less likely to experience acyclovir-resistant HSV infection compared with those who received episodic therapy for outbreaks (513).

#### **Genital Herpes During Pregnancy**

Prevention of neonatal herpes depends both on preventing acquisition of genital herpes during late pregnancy and avoiding exposure of the neonate to herpetic lesions and viral shedding during delivery. Mothers of newborns who acquire neonatal herpes often lack histories of clinically evident genital herpes (514,515). The risk for transmission to the neonate from an infected mother is high (30%–50%) among women who acquire genital herpes near the time of delivery and low (<1%) among women with prenatal histories of recurrent herpes or who acquire genital herpes during the first half of pregnancy (516,517). Women who acquire HSV in the second half of pregnancy should be managed in consultation with maternal-fetal medicine and infectious disease specialists.

All pregnant women should be asked whether they have a history of genital herpes or genital symptoms concerning for HSV infection. At the onset of labor, all women should be questioned thoroughly about symptoms of genital herpes, including prodromal symptoms (e.g., pain or burning at site before appearance of lesion), and all women should be examined thoroughly for herpetic lesions. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally. Although cesarean delivery does not eliminate the risk for HSV transmission to the neonate (517), women with recurrent genital herpetic lesions at the onset of labor should have a cesarean delivery to reduce the risk for neonatal HSV infection.

Routine HSV-2 serologic screening of pregnant women is not recommended. Women without known genital herpes should be counseled to abstain from vaginal intercourse during the third trimester with partners known to have or suspected of having genital herpes. In addition, to prevent HSV-1 genital herpes, pregnant women without known orolabial herpes should be advised to abstain from receptive oral sex during the third trimester with partners known to have or suspected to have orolabial herpes. Type-specific serologic tests can be useful for identifying pregnant women at risk for HSV infection and for guiding counseling regarding the risk for acquiring genital

herpes during pregnancy. For example, such testing might be offered to a woman with no history of genital herpes whose sex partner has HSV infection. Many fetuses are exposed to acyclovir each year, and the medication is believed to be safe for use during all trimesters of pregnancy. A case-control study reported an increased risk for the rare neonatal outcome of gastroschisis among women who used antiviral medications between the month before conception and the third month of pregnancy (518). Acyclovir is also believed to be safe during breastfeeding (431,519). Although data regarding prenatal exposure to valacyclovir and famciclovir are limited, data from animal trials indicate that these drugs also pose a low risk among pregnant women (520). Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV (see Genital Herpes, Hepatitis). Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term (521–523). However, such treatment might not protect against transmission to neonates in all cases (524). No data support use of antiviral therapy among asymptomatic HSV-seropositive women without a history of genital herpes. In addition, the effectiveness of antiviral therapy among sex partners with a history of genital herpes to decrease the risk for HSV transmission to a pregnant woman has not been studied. Additional information on the clinical management of genital herpes in pregnancy is available through existing guidelines (525).

#### **Recommended Regimen for Suppression of Recurrent Genital Herpes Among Pregnant Women\***

Acyclovir 400 mg orally 3 times/day

or

Valacyclovir 500 mg orally 2 times/day

\* Treatment recommended starting at 36 weeks' gestation.

clinical signs of neonatal herpes to guide treatment initiation. In addition, administration of acyclovir might be considered for neonates born to women who acquired HSV near term because the risk for neonatal herpes is high for these newborn infants. All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS.

## **Granuloma Inguinale (Donovanosis)**

Granuloma inguinale (donovanosis) is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*). The disease occurs rarely in the United States; however, sporadic cases have been described in India, South Africa, and South America (526–535). Although granuloma inguinale was previously endemic in Australia, it is now extremely rare (536,537). Clinically, the disease is characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudobubo) also might occur. The lesions are highly vascular (i.e., beefy red appearance) and can bleed. Exogenous infection can occur with infection extension to the pelvis, or it can disseminate to intra-abdominal organs, bones, or the mouth. The lesions also can develop secondary bacterial infection and can coexist with other sexually transmitted pathogens.

## **Diagnostic Considerations**

The causative organism of granuloma inguinale is difficult to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy. Although no FDA-cleared molecular tests for the detection of *K. granulomatis* DNA exist, molecular assays might be useful for identifying the causative agent.

## **Treatment**

Multiple antimicrobial regimens have been effective; however, only a limited number of controlled trials have been published (538). Treatment has been reported to halt progression of lesions, and healing typically proceeds inward from the ulcer margins. Prolonged therapy is usually required to permit granulation and reepithelialization of the ulcers. Relapse can occur 6–18 months after apparently effective therapy.

**Recommended Regimen for Granuloma Inguinale (Donovanosis)**

**Azithromycin** 1 g orally once weekly or 500 mg daily for >3 weeks and until all lesions have completely healed

**Alternative Regimens**

**Doxycycline** 100 mg orally 2 times/day for at least 3 weeks and until all lesions have completely healed

or

**Erythromycin base** 500 mg orally 4 times/day for >3 weeks and until all lesions have completely healed

or

**Trimethoprim-sulfamethoxazole** one double-strength (160 mg/800 mg) tablet orally 2 times/day for >3 weeks and until all lesions have completely healed

The addition of another antibiotic to these regimens can be considered if improvement is not evident within the first few days of therapy.

**Other Management Considerations**

Patients should be followed clinically until signs and symptoms have resolved. All persons who receive a diagnosis of granuloma inguinale should be tested for HIV.

**Follow-Up**

Patients should be followed clinically until signs and symptoms resolve.

**Management of Sex Partners**

Persons who have had sexual contact with a patient who has granuloma inguinale within the 60 days before onset of the patient's symptoms should be examined and offered therapy. However, the value of empiric therapy in the absence of clinical signs and symptoms has not been established.

**Special Considerations****Pregnancy**

Use of doxycycline in pregnancy might be associated with discoloration of teeth; however, the risk is not well defined. Doxycycline is compatible with breastfeeding (431). Sulfonamides can be associated with neonatal kernicterus among those with glucose-6-phosphate dehydrogenase deficiency and should be avoided during the third trimester and while breastfeeding (431). For these reasons, pregnant and lactating women with granuloma inguinale should be treated with a macrolide regimen (erythromycin or azithromycin).

**HIV Infection**

Persons with granuloma inguinale and HIV infection should receive the same regimens as those who do not have HIV.

**Lymphogranuloma Venereum**

LGV is caused by *C. trachomatis* serovars L1, L2, or L3 (539,540). LGV can cause severe inflammation and invasive infection, in contrast with *C. trachomatis* serovars A–K that cause mild or asymptomatic infection. Clinical manifestations of LGV can include GUD, lymphadenopathy, or proctocolitis. Rectal exposure among MSM or women can result in proctocolitis, which is the most common presentation of LGV infection (541), and can mimic inflammatory bowel disease with clinical findings of mucoid or hemorrhagic rectal discharge, anal pain, constipation, fever, or tenesmus (542,543). Outbreaks of LGV proctocolitis have been reported among MSM with high rates of HIV infection (544–547). LGV proctocolitis can be an invasive, systemic infection and, if it is not treated early, can lead to chronic colorectal fistulas and strictures; reactive arthropathy has also been reported. However, reports indicate that rectal LGV can also be asymptomatic (548). A common clinical manifestation of LGV among heterosexuals is tender inguinal or femoral lymphadenopathy that is typically unilateral. A self-limited genital ulcer or papule sometimes occurs at the site of inoculation. However, by the time persons seek care, the lesions have often disappeared. LGV-associated lymphadenopathy can be severe, with bubo formation from fluctuant or suppurative inguinal or femoral lymphadenopathy. Oral ulceration can occur and might be associated with cervical adenopathy (549–551). Persons with genital or colorectal LGV lesions can also experience secondary bacterial infection or can be infected with other sexually and nonsexually transmitted pathogens.

**Diagnostic Considerations**

A definitive LGV diagnosis can be made only with LGV-specific molecular testing (e.g., PCR-based genotyping). These tests can differentiate LGV from non-LGV *C. trachomatis* in rectal specimens. However, these tests are not widely available, and results are not typically available in a time frame that would influence clinical management. Therefore, diagnosis is based on clinical suspicion, epidemiologic information, and a *C. trachomatis* NAAT at the symptomatic anatomic site, along with exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital, oral, or rectal ulcers (551,552). Genital or oral lesions, rectal specimens, and lymph node specimens (i.e., lesion swab or bubo aspirate) can be tested for *C. trachomatis* by NAAT or culture. NAAT is the preferred approach for testing because it can detect both LGV strains and non-LGV *C. trachomatis* strains (553). Therefore, all persons presenting with proctocolitis should be tested for chlamydia with a NAAT performed on rectal specimens. Severe symptoms of proctocolitis (e.g., bloody discharge, tenesmus, and rectal

ulcers) indicate LGV. A rectal Gram stain with >10 white blood cells (WBCs) has also been associated with rectal LGV (545,554,555).

Chlamydia serology (complement fixation or microimmunofluorescence) should not be used routinely as a diagnostic tool for LGV because the utility of these serologic methods has not been established, interpretation has not been standardized, and validation for clinical proctitis presentation has not been done. It might support an LGV diagnosis in cases of isolated inguinal or femoral lymphadenopathy for which diagnostic material for *C. trachomatis* NAAT cannot be obtained.

## Treatment

At the time of the initial visit (before diagnostic NAATs for chlamydia are available), persons with a clinical syndrome consistent with LGV should be presumptively treated. Presumptive treatment for LGV is indicated among patients with symptoms or signs of proctocolitis (e.g., bloody discharge, tenesmus, or ulceration); in cases of severe inguinal lymphadenopathy with bubo formation, particularly if the patient has a recent history of a genital ulcer; or in the presence of a genital ulcer if other etiologies have been ruled out. The goal of treatment is to cure infection and prevent ongoing tissue damage, although tissue reaction to the infection can result in scarring. Buboies might require aspiration through intact skin or incision and drainage to prevent formation of inguinal or femoral ulcerations.

### Recommended Regimen for Lymphogranuloma Venereum

Doxycycline 100 mg orally 2 times/day for 21 days

### Alternative Regimens

Azithromycin 1 g orally once weekly for 3 weeks\*

or

Erythromycin base 500 mg orally 4 times/day for 21 days

\* Because this regimen has not been validated, a test of cure with *C. trachomatis* NAAT 4 weeks after completion of treatment can be considered.

The optimal treatment duration for symptomatic LGV has not been studied in clinical trials. The recommended 21-day course of doxycycline is based on long-standing clinical practice and is highly effective, with an estimated cure rate of >98.5% (555,556). Shorter courses of doxycycline might be effective on the basis of a small retrospective study of MSM with rectal LGV, 50% of whom were symptomatic, who received a 7- to 14-day course of doxycycline and had a 97% cure rate (558). Randomized prospective studies of shorter-course doxycycline for treating LGV are needed. Longer courses of therapy might be required in the setting of fistulas, buboies, and other forms of severe disease (559).

A small nonrandomized study from Spain involving patients with rectal LGV demonstrated cure rates of 97% with a regimen of azithromycin 1 g once weekly for 3 weeks (560). Pharmacokinetic data support this dosing strategy (561); however, this regimen has not been validated. Fluoroquinolone-based treatments also might be effective; however, the optimal duration of treatment has not been evaluated. The clinical significance of asymptomatic LGV is unknown, and it is effectively treated with a 7-day course of doxycycline (562).

## Other Management Considerations

Patients should be followed clinically until signs and symptoms have resolved. Persons who receive an LGV diagnosis should be tested for other STIs, especially HIV, gonorrhea, and syphilis. Those whose HIV test results are negative should be offered HIV PrEP.

## Follow-Up

All persons who have been treated for LGV should be retested for chlamydia approximately 3 months after treatment. If retesting at 3 months is not possible, providers should retest at the patient's next visit for medical care within the 12-month period after initial treatment.

## Management of Sex Partners

Persons who have had sexual contact with a patient who has LGV within the 60 days before onset of the patient's symptoms should be evaluated, examined, and tested for chlamydial infection, depending on anatomic site of exposure. Asymptomatic partners should be presumptively treated with a chlamydia regimen (doxycycline 100 mg orally 2 times/day for 7 days).

## Special Considerations

### Pregnancy

Use of doxycycline in pregnancy might be associated with discoloration of teeth; however, the risk is not well defined (563). Doxycycline is compatible with breastfeeding (431). Azithromycin might prove useful for LGV treatment during pregnancy, at a presumptive dose of 1 g weekly for 3 weeks; no published data are available regarding an effective dose and duration of treatment. Pregnant and lactating women with LGV can be treated with erythromycin, although this regimen is associated with frequent gastrointestinal side effects. Pregnant women treated for LGV should have a test of cure performed 4 weeks after the initial *C. trachomatis* NAAT-positive test.

## HIV Infection

Persons with LGV and HIV infection should receive the same regimens as those who do not have HIV. Prolonged therapy might be required because a delay in resolution of symptoms might occur.

## Syphilis

Syphilis is a systemic disease caused by *T. pallidum*. The disease has been divided into stages on the basis of clinical findings, which guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms. Primary syphilis classically presents as a single painless ulcer or chancre at the site of infection but can also present with multiple, atypical, or painful lesions (564). Secondary syphilis manifestations can include skin rash, mucocutaneous lesions, and lymphadenopathy. Tertiary syphilis can present with cardiac involvement, gummatous lesions, tabes dorsalis, and general paresis.

Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are classified as late latent syphilis or latent syphilis of unknown duration.

*T. pallidum* can infect the CNS, which can occur at any stage of syphilis and result in neurosyphilis. Early neurologic clinical manifestations or syphilitic meningitis (e.g., cranial nerve dysfunction, meningitis, meningocephalitis, stroke, and acute altered mental status) are usually present within the first few months or years of infection. Late neurologic manifestations (e.g., tabes dorsalis and general paresis) occur 10 to >30 years after infection.

Infection of the visual system (ocular syphilis) or auditory system (otosyphilis) can occur at any stage of syphilis but is commonly identified during the early stages and can present with or without additional CNS involvement. Ocular syphilis often presents as panuveitis but can involve structures in both the anterior and posterior segment of the eye, including conjunctivitis, anterior uveitis, posterior interstitial keratitis, optic neuropathy, and retinal vasculitis. Ocular syphilis can result in permanent vision loss. Otosyphilis typically presents with cochleo-vestibular symptoms, including tinnitus, vertigo, and sensorineural hearing loss. Hearing loss can be unilateral or bilateral, have a sudden onset, and progress rapidly. Otosyphilis can result in permanent hearing loss.

## Diagnostic Considerations

Darkfield examinations and molecular tests for detecting *T. pallidum* directly from lesion exudate or tissue are the definitive methods for diagnosing early syphilis and congenital syphilis (565). Although no *T. pallidum* direct-detection molecular NAATs are commercially available, certain laboratories provide locally developed and validated PCR tests for detecting *T. pallidum* DNA. A presumptive diagnosis of syphilis requires use of two laboratory serologic tests: a nontreponemal test (i.e., Venereal Disease Research Laboratory [VDRL] or rapid plasma reagent [RPR] test) and a treponemal test (i.e., the *T. pallidum* passive particle agglutination [TP-PA] assay, various EIAs, chemiluminescence immunoassays [CIAs] and immunoblots, or rapid treponemal assays) (566–568). At least 18 treponemal-specific tests are cleared for use in the United States. Use of only one type of serologic test (nontreponemal or treponemal) is insufficient for diagnosis and can result in false-negative results among persons tested during primary syphilis and false-positive results among persons without syphilis or previously treated syphilis.

### Nontreponemal Tests and Traditional Algorithm

False-positive nontreponemal test results can be associated with multiple medical conditions and factors unrelated to syphilis, including other infections (e.g., HIV), autoimmune conditions, vaccinations, injecting drug use, pregnancy, and older age (566,569). Therefore, persons with a reactive nontreponemal test should always receive a treponemal test to confirm the syphilis diagnosis (i.e., traditional algorithm). Nontreponemal test antibody titers might correlate with disease activity and are used for monitoring treatment response. Serum should be diluted to identify the highest titer, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary for demonstrating a clinically significant difference between two nontreponemal test results obtained by using the same serologic test, preferably from the same manufacturer to avoid variation in results. Sequential serologic tests for a patient should be performed using the same testing method (VDRL or RPR), preferably by the same laboratory. VDRL and RPR are equally valid assays; however, quantitative results from the two tests cannot be compared directly with each other because the methods are different, and RPR titers frequently are slightly higher than VDRL titers.

Nontreponemal test titers usually decrease after treatment and might become nonreactive with time. However, for certain persons, nontreponemal antibodies might decrease less than fourfold after treatment (i.e., inadequate serologic response) or might decline appropriately but fail to serorevert and

persist for a long period. Atypical nontreponemal serologic test results (e.g., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV status. When serologic tests do not correspond with clinical findings indicative of primary, secondary, or latent syphilis, presumptive treatment is recommended for persons with risk factors for syphilis, and use of other tests (e.g., biopsy for histology and immunostaining and PCR of lesion) should be considered. For the majority of persons with HIV infection, serologic tests are accurate and reliable for diagnosing syphilis and evaluating response to treatment.

### **Treponemal Tests and Reverse Sequence Algorithm**

The majority of patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of adequate treatment or disease activity. However, 15%–25% of patients treated during the primary stage revert to being serologically nonreactive after 2–3 years (570). Treponemal antibody titers do not predict treatment response and therefore should not be used for this purpose.

Clinical laboratories sometimes screen syphilis serologic samples by using automated treponemal immunoassays, typically by EIA or CIA (571–573). This reverse sequence algorithm for syphilis testing can identify persons previously treated for syphilis, those with untreated or incompletely treated syphilis, and those with false-positive results that can occur with a low likelihood of infection (574). Persons with a positive treponemal screening test should have a standard quantitative nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions. If the nontreponemal test is negative, the laboratory should perform a treponemal test different from the one used for initial testing, preferably TP-PA or treponemal assay based on different antigens than the original test, to adjudicate the results of the initial test.

If a second treponemal test is positive (e.g., EIA reactive, RPR nonreactive, or TP-PA reactive), persons with a history of previous treatment will require no further management unless sexual history indicates a reexposure. In this instance, a repeat nontreponemal test 2–4 weeks after a confirmed medical history and physical examination is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless a medical history or results of a physical examination indicate a recent infection, previously untreated persons should be treated for syphilis of unknown duration or late latent syphilis.

If the second treponemal test is negative (e.g., EIA reactive, RPR nonreactive, TP-PA nonreactive) and the epidemiologic

risk and clinical probability for syphilis are low, further evaluation or treatment is not indicated.

Multiple studies demonstrate that high quantitative index values or high signal-to-cutoff ratio from treponemal EIA or CIA tests correlate with TP-PA positivity, which might eliminate the need for additional confirmatory testing; however, the range of index values varies among different treponemal immunoassays, and the values that correspond to high levels of reactivity with confirmatory testing might differ by immunoassay (567,575–582).

### **Cerebrospinal Fluid Evaluation**

Further testing with CSF evaluation is warranted for persons with clinical signs of neurosyphilis (e.g., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, or loss of vibration sense). All patients with ocular symptoms and reactive syphilis serology need a full ocular examination, including cranial nerve evaluation. If cranial nerve dysfunction is present, a CSF evaluation is needed. Among persons with isolated ocular symptoms (i.e., no cranial nerve dysfunction or other neurologic abnormalities), confirmed ocular abnormalities on examination, and reactive syphilis serology, a CSF examination is unnecessary before treatment. CSF analysis can be helpful in evaluating persons with ocular symptoms and reactive syphilis serology who do not have ocular findings or cranial nerve dysfunction on examination. Among patients with isolated auditory abnormalities and reactive syphilis serology, CSF evaluation is likely to be normal and is unnecessary before treatment (583,584).

Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. Diagnosis of neurosyphilis depends on a combination of CSF tests (e.g., CSF cell count, protein, or reactive CSF-VDRL) in the presence of reactive serologic test (nontreponemal and treponemal) results and neurologic signs and symptoms. CSF laboratory abnormalities are common for persons with early syphilis and are of unknown medical significance in the absence of neurologic signs or symptoms (585). CSF-VDRL is highly specific but insensitive. For a person with neurologic signs or symptoms, a reactive CSF-VDRL (in the absence of blood contamination) is considered diagnostic of neurosyphilis.

When CSF-VDRL is negative despite clinical signs of neurosyphilis, reactive serologic test results, lymphocytic pleocytosis, or protein, neurosyphilis should be considered. In that instance, additional evaluation by using fluorescent treponemal-antibody absorption (FTA-ABS) or TP-PA testing on CSF might be warranted. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Fewer data are available regarding CSF TP-PA;

however, the sensitivity and specificity appear similar to the CSF FTA-ABS (586). Neurosyphilis is highly unlikely with a negative CSF FTA-ABS or TP-PA test, especially among persons with nonspecific neurologic signs and symptoms (587).

Among persons with HIV infection, CSF leukocyte count can be elevated ( $>5$  WBCs/mm $^3$ ); the association with CSF leukocyte count and plasma HIV viral suppression has not been well characterized. Using a higher cutoff ( $>20$  WBCs/mm $^3$ ) might improve the specificity of neurosyphilis diagnosis among this population (588).

## Treatment

Penicillin G, administered parenterally, is the preferred drug for treating patients in all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), dosage, and length of treatment depend on the stage and clinical manifestations of the disease. Treatment for late latent syphilis ( $>1$  years' duration) and tertiary syphilis requires a longer duration of therapy because organisms theoretically might be dividing more slowly (the validity of this rationale has not been assessed). Longer treatment duration is required for persons with latent syphilis of unknown duration to ensure that those who did not acquire syphilis within the preceding year are adequately treated.

Selection of the appropriate penicillin preparation is important because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by certain forms of penicillin. Combinations of benzathine penicillin, procaine penicillin, and oral penicillin preparations are not considered appropriate for syphilis treatment. Reports have indicated that practitioners have inadvertently prescribed combination long- and short-acting benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin product (Bicillin L-A) recommended in the United States for treating primary, secondary, and latent syphilis. Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products to avoid using the incorrect combination therapy agent for treating syphilis (589).

Penicillin's effectiveness for treating syphilis was well established through clinical experience even before the value of randomized controlled clinical trials was recognized. Therefore, approximately all recommendations for treating syphilis are based not only on clinical trials and observational studies, but on many decades of clinical experience.

## Special Considerations

### Pregnancy

Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis at any stage who report penicillin allergy should be desensitized and treated with penicillin (see Management of Persons Who Have a History of Penicillin Allergy).

### Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, and fever that can occur within the first 24 hours after the initiation of any syphilis therapy; it is a reaction to treatment and not an allergic reaction to penicillin. Patients should be informed about this possible adverse reaction and how to manage it if it occurs. The Jarisch-Herxheimer reaction occurs most frequently among persons who have early syphilis, presumably because bacterial loads are higher during these stages. Antipyretics can be used to manage symptoms; however, they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women; however, this should not prevent or delay therapy (590) (see Syphilis During Pregnancy).

### Management of Sex Partners

Sexual transmission of *T. pallidum* is thought to occur only when mucocutaneous syphilitic lesions are present. Such manifestations are uncommon after the first year of infection. Persons exposed through sexual contact with a person who has primary, secondary, or early latent syphilis should be evaluated clinically and serologically and treated according to the following recommendations:

- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis  $<90$  days before the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative.
- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis  $>90$  days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and syphilis stage.
- In certain areas or among populations with high syphilis infection rates, health departments recommend notification and presumptive treatment of sex partners of persons with

syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., >1:32) because high titers might be indicative of early syphilis. These partners should be managed as if the index patient had early syphilis.

- Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings.
- The following sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, within 6 months plus duration of symptoms for those with secondary syphilis, and within 1 year for persons with early latent syphilis.

## Primary and Secondary Syphilis

### Treatment

Parenteral penicillin G has been used effectively for achieving clinical resolution (i.e., the healing of lesions and prevention of sexual transmission) and for preventing late sequelae. However, no comparative trials have been conducted to guide selection of an optimal penicillin regimen. Substantially fewer data are available for nonpenicillin regimens.

#### Recommended Regimen for Primary and Secondary Syphilis\* Among Adults

Benzathine penicillin G 2.4 million units IM in a single dose

\* Recommendations for treating syphilis among persons with HIV infection and pregnant women are discussed elsewhere in this report (see Syphilis Among Persons with HIV Infection; Syphilis During Pregnancy).

Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy of this recommended regimen when used to treat primary and secondary syphilis, regardless of HIV status (591–593).

#### Recommended Regimen for Syphilis Among Infants and Children

Benzathine penicillin G 50,000 units/kg body weight IM, up to the adult dose of 2.4 million units in a single dose

Infants and children aged ≥1 month who receive a syphilis diagnosis should have birth and maternal medical records reviewed to assess whether they have congenital or acquired syphilis (see Congenital Syphilis). Infants and children aged ≥1 month with primary and secondary syphilis should be managed by a pediatric infectious disease specialist and evaluated for sexual abuse (e.g., through consultation with child protective services) (see Sexual Assault or Abuse of Children).

## Other Management Considerations

All persons who have primary and secondary syphilis should be tested for HIV at the time of diagnosis and treatment. Those persons whose HIV test results are negative should be offered HIV PrEP. In geographic areas in which HIV prevalence is high, persons who have primary or secondary syphilis should be offered PrEP and retested for HIV in 3 months if the initial HIV test result was negative.

Persons who have syphilis and symptoms or signs indicating neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke, or altered mental state) should have an evaluation that includes CSF analysis. Persons with syphilis who have symptoms or signs of ocular syphilis (e.g., uveitis, iritis, neuroretinitis, or optic neuritis) should have a thorough cranial nerve examination and ocular slit-lamp and ophthalmologic examinations. CSF evaluation is not always needed for persons with ocular syphilis if no evidence of cranial nerves 2, 3, 4, 5, and 6 dysfunction or other evidence of neurologic disease exists. If symptoms and signs of otic syphilis are present then an otologic examination is needed; CSF evaluation in persons with otic syphilis does not aid in the clinical management and therefore is not recommended (see Cerebrospinal Fluid Evaluation). Treatment should be guided by the results of these evaluations. Invasion of CSF by *T. pallidum* accompanied by CSF laboratory abnormalities is common among adults who have primary or secondary syphilis but has unknown medical significance (585). In the absence of clinical neurologic findings, no evidence supports variation from the recommended treatment regimen for primary or secondary syphilis. Symptomatic neurosyphilis after treatment with the penicillin regimens recommended for primary and secondary syphilis is rare. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

### Follow-Up

Clinical and serologic evaluation should be performed at 6 and 12 months after treatment; more frequent evaluation might be prudent if opportunity for follow-up is uncertain or if repeat infection is a clinical concern. Serologic response (i.e., titer) should be compared with the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, and definitive criteria for cure or failure by serologic criteria have not been well established. In addition, nontreponemal test titers might decrease more slowly for persons previously treated for syphilis (594,595).

Persons who have signs or symptoms that persist or recur and those with at least a fourfold increase in nontreponemal

test titer persisting for >2 weeks likely were reinfected or experienced treatment failure. Among persons who have neurologic findings or persons with no neurologic findings without any reported sexual exposure during the previous 3–6 months indicating that treatment failure might be possible, a CSF examination is recommended with treatment guided by CSF findings. These persons should also be reevaluated for HIV infection.

Among persons with no neurologic findings after a thorough neurologic examination and who are sexually active, reinfection is likely and repeat treatment for early syphilis is recommended. These persons should also be reevaluated for HIV infection.

Failure of nontreponemal test titers to decrease fourfold within 12 months after therapy for primary or secondary syphilis (inadequate serologic response) might be indicative of treatment failure. However, clinical trial data have demonstrated that 10%–20% of persons with primary and secondary syphilis treated with the recommended therapy will not achieve the fourfold decrease in nontreponemal titer within 12 months after treatment (591,596,597). Serologic response to treatment appears to be associated with multiple factors, including the person's syphilis stage (earlier stages are more likely to decrease fourfold and become nonreactive), initial nontreponemal antibody titers (titers <1:8 are less likely to decline fourfold than higher titers), and age (titers among older patients might be less likely to decrease fourfold than those of younger patients) (596–598). Optimal management of persons who have an inadequate serologic response after syphilis treatment is unclear. At a minimum, these persons should receive additional neurologic examinations, clinical and serologic follow-up annually, and reevaluation for HIV infection. If neurologic symptoms or signs are identified, a CSF evaluation is recommended, with findings guiding management. If additional follow-up cannot be ensured, retreatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in situations in which follow-up is uncertain.

For retreatment, weekly injections of benzathine penicillin G 2.4 million units intramuscularly (IM) for 3 weeks is recommended, unless CSF examination indicates that neurosyphilis is present (see Neurosyphilis, Ocular Syphilis, and Otosyphilis). Serologic titers might not decrease, despite a negative CSF examination and a repeated 3-week therapy course (599). In these circumstances, the benefit of additional therapy or repeated CSF examinations is unclear, and it is not typically recommended. Serologic and clinical monitoring at least annually should continue to monitor for any sustained increases in nontreponemal titer.

## Management of Sex Partners

See Syphilis, Management of Sex Partners.

## Special Considerations

### Penicillin Allergy

Data to support use of alternatives to penicillin in treating primary and secondary syphilis are limited. However, multiple therapies might be effective for nonpregnant persons with penicillin allergy who have primary or secondary syphilis. Doxycycline (100 mg orally 2 times/day for 14 days) (600,601) and tetracycline (500 mg orally 4 times/day for 14 days) have been used for years and can be effective. Compliance is likely to be better with doxycycline than tetracycline because tetracycline can cause more gastrointestinal side effects and requires more frequent dosing. Limited clinical studies, along with biologic and pharmacologic evidence, indicate that ceftriaxone (1 g daily either IM or IV for 10 days) is effective for treating primary and secondary syphilis; however, the optimal dose and duration of ceftriaxone therapy have not been defined (602,603). Azithromycin as a single 2-g oral dose has been effective for treating primary and secondary syphilis among certain populations (602,604,605). However, because of *T. pallidum* chromosomal mutations associated with azithromycin and other macrolide resistance and documented treatment failures in multiple U.S. geographic areas, azithromycin should not be used as treatment for syphilis (606–608). Thorough clinical and serologic follow-up of persons receiving any alternative therapy is essential.

Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G. Skin testing for penicillin allergy might be useful in circumstances in which the reagents and expertise are available for performing the test adequately (see Management of Persons Who Have a History of Penicillin Allergy).

### Pregnancy

Pregnant women with primary or secondary syphilis who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy; Syphilis During Pregnancy).

### HIV Infection

Persons with HIV infection who have primary or secondary syphilis should be treated similarly to those without HIV (see Syphilis Among Persons with HIV Infection).

## Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of primary, secondary, or tertiary disease. Persons who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis (early nonprimary, nonsecondary). Persons can receive a diagnosis of early latent syphilis if, during the year preceding the diagnosis, they had a documented seroconversion or a sustained (>2 weeks) fourfold or greater increase in nontreponemal test titers in a previously treated person; unequivocal symptoms of primary or secondary syphilis; or a sex partner documented to have primary, secondary, or early latent syphilis. In addition, for persons with reactive nontreponemal and treponemal tests whose only possible exposure occurred during the previous 12 months, early latent syphilis can be assumed.

In the absence of these conditions associated with latent syphilis, an asymptomatic person should be considered to have latent syphilis of unknown duration or late latent syphilis (>1 year's duration). Nontreponemal serologic titers usually are higher early in the course of syphilis infection. However, early latent syphilis cannot be reliably diagnosed solely on the basis of nontreponemal titers. All persons with latent syphilis should have careful examination of all accessible mucosal surfaces to evaluate for mucosal lesions (primary or secondary syphilis) before making a latent syphilis diagnosis. Physical examination should include the oral cavity, perianal area, perineum, rectum, and genitals (vagina and cervix for women; scrotum, penis, and underneath the foreskin for uncircumcised men).

### Treatment

Because latent syphilis is not transmitted sexually, the objective of treating persons in this disease stage is to prevent medical complications of syphilis. Latent syphilis can also be vertically transmitted to a fetus; therefore, the goal of treating a pregnant woman is to prevent congenital syphilis. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available for guiding choice of specific regimens or duration. Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV status (592,593,609).

#### Recommended Regimens for Latent Syphilis\* Among Adults

**Early latent syphilis:** Benzathine penicillin G 2.4 million units IM in a single dose

**Late latent syphilis:** Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

\* Recommendations for treating syphilis in persons with HIV and pregnant women are discussed elsewhere in this report (see Syphilis Among Persons with HIV Infection; Syphilis During Pregnancy).

Infants and children aged ≥1 month with diagnosed latent syphilis should be managed by a pediatric infectious disease specialist and receive a CSF examination. In addition, birth and maternal medical records should be reviewed to assess whether these infants and children have congenital or acquired syphilis. For those with congenital syphilis, treatment should be undertaken as described (see Congenital Syphilis). Those with acquired syphilis should be evaluated for sexual abuse (e.g., through consultation with child protection services) (see Sexual Assault or Abuse of Children). These regimens are for children who are not allergic to penicillin who have acquired syphilis and who have normal CSF examinations.

### Other Management Considerations

All persons who have latent syphilis should be tested for HIV at the time of diagnosis or treatment. Those persons whose HIV test results are negative should be offered HIV PrEP. In geographic areas in which the prevalence of HIV infection is high or among populations vulnerable to HIV acquisition, persons who have early latent or late latent syphilis should be offered PrEP and retested for HIV in 3 months if the first HIV test result was negative.

Persons who receive a diagnosis of latent syphilis and have neurologic or ocular signs and symptoms (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, or symptoms or signs of meningitis or stroke) should be evaluated for neurosyphilis, ocular syphilis, or otosyphilis according to their clinical presentation (see Neurosyphilis, Ocular Syphilis, and Otitis Syphilis).

If a person receives a delayed dose of penicillin in a course of weekly therapy for late latent syphilis or syphilis of unknown duration, the course of action that should be recommended is unclear. Clinical experience indicates that an interval of 10–14 days between doses of benzathine penicillin for latent syphilis might be acceptable before restarting the sequence of injections (i.e., if dose 1 is administered on day 0, dose 2 is administered on days 10–14). Pharmacologic considerations indicate that an interval of 7–9 days between doses, if feasible, might be preferred (610–612). Delayed doses are not optimal for pregnant women receiving therapy for latent syphilis (613). Pregnant women who have delays in any therapy dose >9 days between doses should repeat the full course of therapy.

### Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. These serologic titers should be compared with the titer at the time of treatment. Persons with at least a fourfold sustained increase in nontreponemal test titer persisting for >2 weeks or who experienced signs or symptoms attributable to primary or secondary syphilis

were likely reinfected or experienced treatment failure. These persons should be retreated and reevaluated for HIV infection. Among persons who have neurologic findings after a thorough neurologic examination or among persons with no neurologic findings and no sexual exposure during the previous year, a CSF examination is recommended. Treatment should be guided by CSF findings. Among persons with no neurologic findings after neurologic examination and who are sexually active, treatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended.

Optimal management of persons who have less than a fourfold decrease in titers 24 months after treatment (i.e., an inadequate serologic response) is unclear, especially if the initial titer was <1:8. At a minimum, these persons should receive additional clinical and serologic follow-up and be evaluated for HIV infection. If neurologic symptoms or signs are identified, a CSF evaluation is recommended, with the findings guiding management. If additional follow-up cannot be ensured or if an initially high titer (>1:32) does not decrease at least fourfold 24 months after treatment, retreatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in such situations where follow-up is uncertain or initial high titers do not decrease after 24 months.

If the CSF examination is negative, repeat treatment for latent syphilis is recommended. Serologic titers might not decrease despite a negative CSF examination and a repeated course of therapy, especially if the initial nontreponemal titer is low (<1:8); in these circumstances, the need for additional therapy or repeated CSF examinations is unclear but is usually not recommended. Serologic and clinical monitoring at least annually should continue to monitor for any sustained increases in nontreponemal titer.

## Management of Sex Partners

See Syphilis, Management of Sex Partners.

## Special Considerations

### Penicillin Allergy

The effectiveness of alternatives to penicillin in treating latent syphilis has not been well documented. Nonpregnant patients allergic to penicillin who have clearly defined early latent syphilis should respond to antibiotics recommended as alternatives to penicillin for treating primary and secondary syphilis (see Primary and Secondary Syphilis). The only acceptable alternatives for treating late latent syphilis or syphilis of unknown duration are doxycycline (100 mg orally 2 times/day) or tetracycline (500 mg orally 4 times/day),

each for 28 days. The efficacy of these alternative regimens among persons with HIV infection has not been well studied. These therapies should be used only in conjunction with close serologic and clinical follow-up, especially among persons with HIV infection. On the basis of biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating latent syphilis. However, the optimal dose and duration of ceftriaxone therapy have not been defined; treatment decisions should be discussed in consultation with a specialist. Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G. Skin testing for penicillin allergy might be useful in circumstances in which the reagents and expertise are available for performing the test adequately (see Management of Persons Who Have a History of Penicillin Allergy).

### Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing for penicillin allergy might be useful in circumstances in which the reagents and expertise are available for performing the test adequately (see Management of Persons Who Have a History of Penicillin Allergy; Syphilis During Pregnancy).

### HIV Infection

Persons with HIV infection who have latent syphilis should be treated similarly to persons who do not have HIV (see Syphilis Among Persons with HIV Infection).

## Tertiary Syphilis

Tertiary syphilis refers to gummas, cardiovascular syphilis, psychiatric manifestations (e.g., memory loss or personality changes), or late neurosyphilis. Guidelines for all forms of neurosyphilis (e.g., early or late neurosyphilis) are discussed elsewhere in these recommendations (see Neurosyphilis, Ocular Syphilis, and Otosyphilis). Persons with gummas and cardiovascular syphilis who are not allergic to penicillin and have no evidence of neurosyphilis by clinical and CSF examination should be treated with the following regimen.

### Recommended Regimen for Tertiary Syphilis Among Adults

**Tertiary syphilis with normal CSF examination:** Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

## Other Management Considerations

All persons who have tertiary syphilis should receive a CSF examination before therapy is initiated and have an HIV test.

Those persons whose HIV test results are negative should be offered HIV PrEP. Persons with CSF abnormalities should be treated with a neurosyphilis regimen. Certain providers treat all persons who have cardiovascular syphilis with a neurosyphilis regimen. These persons should be managed in consultation with an infectious disease specialist. Limited information is available concerning clinical response and follow-up of persons who have tertiary syphilis.

## Management of Sex Partners

See Syphilis, Management of Sex Partners.

## Special Considerations

### Penicillin Allergy

Any person allergic to penicillin should be treated in consultation with an infectious disease specialist.

### Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy; Syphilis During Pregnancy).

### HIV Infection

Persons with HIV infection who have tertiary syphilis should be treated as described for persons without HIV (see Syphilis Among Persons with HIV Infection).

## Neurosyphilis, Ocular Syphilis, and Otosyphilis

### Treatment

CNS involvement can occur during any stage of syphilis, and CSF laboratory abnormalities are common among persons with early syphilis, even in the absence of clinical neurologic findings. No evidence exists to support variation from recommended diagnosis and treatment for syphilis at any stage for persons without clinical neurologic findings, except tertiary syphilis. If clinical evidence of neurologic involvement is observed (e.g., cognitive dysfunction, motor or sensory deficits, cranial nerve palsies, or symptoms or signs of meningitis or stroke), a CSF examination should be performed before treatment.

Syphilitic uveitis or other ocular syphilis manifestations (e.g., neuroretinitis and optic neuritis) can occur at any stage of syphilis and can be isolated abnormalities or associated with neurosyphilis. All persons with ocular symptoms and reactive

syphilis serology need a full ocular examination, including cranial nerve evaluation. If cranial nerve dysfunction is present, a CSF evaluation is needed. Among persons with isolated ocular symptoms (no cranial nerve dysfunction or other neurologic abnormalities), reactive syphilis serology, and confirmed ocular abnormalities on examination, CSF examination is unnecessary before treatment. CSF analysis might be helpful in evaluating persons with ocular symptoms and reactive syphilis serology who do not have ocular findings on examination. If ocular syphilis is suspected, immediate referral to and management in collaboration with an ophthalmologist is crucial. Ocular syphilis should be treated similarly to neurosyphilis, even if a CSF examination is normal.

Hearing loss and other otologic symptoms can occur at any stage of syphilis and can be isolated abnormalities or associated with neurosyphilis, especially of cranial nerve 8. However, among persons with isolated auditory symptoms, normal neurologic examination, and reactive syphilis serology, CSF examination is likely to be normal and is not recommended before treatment. Otosyphilis should be managed in collaboration with an otolaryngologist and treated by using the same regimen as for neurosyphilis.

### Recommended Regimen for Neurosyphilis, Ocular Syphilis, or Otosyphilis Among Adults

Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion for 10–14 days

If compliance with therapy can be ensured, the following alternative regimen might be considered.

### Alternative Regimen

Procaine penicillin G 2.4 million units IM once daily  
plus  
Probencid 500 mg orally 4 times/day, both for 10–14 days

The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for 1–3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

## Other Management Considerations

The following are other considerations in the management of persons who have neurosyphilis:

- All persons who have neurosyphilis, ocular syphilis, or otosyphilis should be tested for HIV at the time of diagnosis. Those whose HIV test results are negative should be offered HIV PrEP.

- Although systemic steroids are used frequently as adjunctive therapy for otosyphilis and for ocular syphilis, such drugs have not been proven to be beneficial.

## Follow-Up

Data from two studies indicate that, among immunocompetent persons and persons with HIV infection who are on effective ART, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment (614,615). Therefore, repeated CSF examinations are unnecessary for persons without HIV infection or persons with HIV infection who are on ART and who exhibit serologic and clinical responses after treatment.

## Management of Sex Partners

See Syphilis, Management of Sex Partners.

## Special Considerations

### Penicillin Allergy

Limited data indicate that ceftriaxone 1–2 g daily either IM or IV for 10–14 days can be used as an alternative treatment for persons with neurosyphilis (603,616,617). Cross-sensitivity between ceftriaxone and penicillin can occur; however, the risk for penicillin cross-reactivity between third-generation cephalosporins is negligible (618–621) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding ceftriaxone safety for a patient with neurosyphilis, skin testing should be performed to confirm penicillin allergy and, if necessary, penicillin desensitization in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

### Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy).

### HIV Infection

Persons with HIV infection who have neurosyphilis should be treated as described for persons without HIV (see Syphilis Among Persons with HIV Infection).

## Syphilis Among Persons with HIV Infection

### Diagnostic Considerations

Interpretation of treponemal and nontreponemal serologic tests for persons with HIV infection is the same as for persons without HIV. Although rare, unusual serologic responses have

been observed among persons with HIV infection who have syphilis. The majority of reports have involved posttreatment serologic titers that were higher than expected (i.e., high serofast) or fluctuated, and false-negative serologic test results and delayed appearance of seroreactivity have also been reported (622).

When clinical findings are indicative of syphilis, but serologic tests are nonreactive or their interpretation is unclear, alternative tests (e.g., biopsy of a lesion, darkfield examination, or PCR of lesion material) might be useful for diagnosis. Neurosyphilis, ocular syphilis, and otosyphilis should be considered in the differential diagnosis of neurologic, ocular, and other signs and symptoms among persons with HIV infection.

### Treatment

Persons with HIV infection who have early syphilis might be at increased risk for neurologic complications (623) and might have higher rates of inadequate serologic response with recommended regimens. The magnitude of these risks is not defined precisely but is likely small. Although long-term (>1 year) comparative data are lacking, no treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis among persons with HIV infection than the syphilis regimens recommended for persons without HIV (609). Careful follow-up after therapy is essential. Using ART per current HIV guidelines might improve clinical outcomes among persons coinfected with HIV and syphilis; concerns regarding adequate treatment of syphilis among persons with HIV infection might not apply to those with HIV virologic suppression (624,625).

### Primary and Secondary Syphilis Among Persons with HIV Infection

#### Recommended Regimen for Primary and Secondary Syphilis Among Persons with HIV Infection

Benzathine penicillin G 2.4 million units IM in a single dose

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis among persons with HIV infection do not result in enhanced efficacy (592,593,609).

### Other Management Considerations

The majority of persons with HIV infection respond appropriately to the recommended benzathine penicillin G treatment regimen for primary and secondary syphilis (626). CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) can be common among persons with HIV, even those without syphilis. The clinical and prognostic significance of such CSF laboratory abnormalities among persons with primary and secondary syphilis who lack neurologic symptoms

is unknown. Certain studies have demonstrated that among persons with HIV infection and syphilis, CSF abnormalities are associated with a CD4<sup>+</sup> T-cell count of  $\leq 350$  cells/mL or an RPR titer of  $\geq 1:32$  (614,627). However, CSF examination followed by treatment for neurosyphilis on the basis of laboratory abnormalities has not been associated with improved clinical outcomes in the absence of neurologic signs and symptoms. All persons with HIV infection and primary and secondary syphilis should have a thorough neurologic, ocular, and otic examination (614,622,625). CSF examination should be reserved for those with an abnormal neurologic examination.

### Follow-Up

Persons with HIV infection and primary or secondary syphilis should be evaluated clinically and serologically for possible treatment failure at 3, 6, 9, 12, and 24 months after therapy; those who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or a sustained [ $>2$  weeks] fourfold or greater increase in titer) should be managed in the same manner as persons without HIV infection (i.e., depending on history of sexual activity and on findings of neurologic examination, either repeat treatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks or CSF examination and repeat treatment guided by CSF findings) (see Primary and Secondary Syphilis).

In addition, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 24 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM at weekly intervals for 3 weeks is recommended. Serologic titers might not decrease despite a negative CSF examination and a repeated 3-week course of therapy (599). Especially if the initial nontreponemal titer is low ( $<1:8$ ) in these circumstances, the benefit of additional therapy or repeated CSF examinations is unclear but is not usually recommended. Serologic and clinical monitoring at least annually should continue to monitor for any sustained increases in nontreponemal titer.

### Management of Sex Partners

See Syphilis, Management of Sex Partners.

### Special Considerations

#### *Penicillin Allergy*

Persons with HIV infection who are allergic to penicillin and have primary or secondary syphilis should be managed according to the recommendations for persons without HIV who are allergic to penicillin (see Primary and Secondary Syphilis). Persons with penicillin allergy whose compliance with alternative therapy or follow-up cannot be ensured should

be desensitized and treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy). Using penicillin alternatives has not been well studied among persons with HIV infection; azithromycin is not recommended for persons with HIV and primary or secondary syphilis infection. Alternative therapies should be used only in conjunction with close serologic and clinical follow-up. Persons with HIV and latent syphilis should be treated similarly to persons who do not have HIV (see Latent Syphilis).

### Latent Syphilis Among Persons with HIV Infection

#### **Recommended Regimen for Early Latent Syphilis Among Persons with HIV Infection**

Benzathine penicillin G 2.4 million units IM in a single dose

#### **Recommended Regimen for Late Latent Syphilis or Latent Syphilis of Unknown Duration Among Persons with HIV Infection**

Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1-week intervals

### Other Management Considerations

All persons with HIV and latent syphilis infection should undergo a thorough neurologic, ocular, and otic examination; those with neurologic symptoms or signs should undergo immediate CSF examination. In the absence of neurologic symptoms or signs, CSF examination has not been associated with improved clinical outcomes and therefore is not recommended. Those with ocular or otic symptoms or signs should be evaluated for ocular syphilis and otosyphilis according to those clinical presentations (see Neurosyphilis, Ocular Syphilis, and Otitis Syphilis).

### Follow-Up

Patients with HIV and latent syphilis infection should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. Those persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or a sustained [ $>2$  weeks] fourfold or greater increase in titer) should be managed in the same manner as persons without HIV (i.e., depending on history of sexual activity and on findings of neurologic examination, either repeat treatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks or CSF examination and repeat treatment guided by CSF findings) (see Latent Syphilis).

In addition, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 24 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM at weekly intervals for

3 weeks is recommended. Serologic titers might not decrease despite a negative CSF examination and a repeated 3-week course of therapy (599). Especially if the initial nontreponemal titer is low (<1:8) in these circumstances, the benefit of additional therapy or repeated CSF examinations is unclear but is not usually recommended. Serologic and clinical monitoring at least annually should continue to ensure nontreponemal titers remain stable without any sustained titer increases.

### **Management of Sex Partners**

See Syphilis, Management of Sex Partners.

### **Special Considerations**

#### **Penicillin Allergy**

The efficacy of alternative nonpenicillin regimens for latent syphilis for persons living with HIV infection has not been well studied, and these therapies should be used only in conjunction with close serologic and clinical follow-up. Patients with penicillin allergy whose compliance with alternative therapy or follow-up cannot be ensured should be desensitized and treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy).

### **Neurosyphilis, Ocular Syphilis, and Otic Syphilis Among Persons with HIV Infection**

All persons with HIV and syphilis infection should receive a careful neurologic ocular and otic examination. Persons with HIV infection and neurosyphilis should be treated according to the recommendations for persons with neurosyphilis and without HIV infection (see Neurosyphilis, Ocular Syphilis, and Oto-syphilis).

### **Follow-Up**

Persons with HIV and neurosyphilis infection should be managed according to the recommendations for persons without HIV infection. Serum RPR can be followed for necessary treatment success rather than following CSF parameters (see Neurosyphilis, Ocular Syphilis, and Oto-syphilis). Limited data indicate that changes in CSF parameters might occur more slowly among persons with HIV infection, especially those with more advanced immunosuppression (588,624).

### **Management of Sex Partners**

See Syphilis, Management of Sex Partners.

### **Special Considerations**

#### **Penicillin Allergy**

Persons with HIV who are allergic to penicillin and have neurosyphilis infection should be managed according to the

recommendations for persons without HIV infection with neurosyphilis who are allergic to penicillin (see Neurosyphilis, Ocular Syphilis, and Oto-syphilis). Small observational studies conducted among persons with HIV and neurosyphilis report that ceftriaxone 1–2 g IV daily for 10–14 days might be effective as an alternative agent (628–630). The possibility of cross-sensitivity between ceftriaxone and penicillin exists; however, the risk for penicillin cross-reactivity between third-generation cephalosporins is negligible (619–621,631) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding the safety of ceftriaxone for a person with HIV and neurosyphilis, skin testing should be performed to confirm penicillin allergy and, if necessary, penicillin desensitization in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

### **Syphilis During Pregnancy**

All women should be screened serologically for syphilis at the first prenatal care visit (174), which is mandated by the majority of states (142). Among populations for whom receipt of prenatal care is not optimal, serologic screening and treatment (if serologic test is reactive) should be performed at the time of pregnancy testing (632). Antepartum screening can be performed by manual nontreponemal antibody testing (e.g., RPR) by using the traditional syphilis screening algorithm or by treponemal antibody testing (e.g., immunoassays) using the reverse sequence algorithm.

Pregnant women with positive treponemal screening tests (e.g., EIA, CIA, or immunoblot) should have additional quantitative nontreponemal testing because titers are essential for monitoring treatment response. Serologic testing should also be performed twice during the third trimester: at 28 weeks' gestation and at delivery for pregnant women who live in communities with high rates of syphilis and for women who have been at risk for syphilis acquisition during pregnancy.

Maternal risk factors for syphilis during pregnancy include sex with multiple partners, sex in conjunction with drug use or transactional sex, late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care, methamphetamine or heroin use, incarceration of the woman or her partner, and unstable housing or homelessness (174,633–636). Moreover, as part of the management of pregnant women who have syphilis, providers should obtain information concerning ongoing risk behaviors and treatment of sex partners to assess the risk for reinfection.

Any woman who has a fetal death after 20 weeks' gestation should be tested for syphilis. No mother or neonate should leave the hospital without maternal serologic status having been

documented at least once during pregnancy. Any woman who at the time of delivery has no prenatal care history or has been at risk for syphilis acquisition during pregnancy (e.g., misuses drugs; has had another STI during pregnancy; or has had multiple sex partners, a new partner, or a partner with an STI) should have the results of a syphilis serologic test documented before discharge.

## Diagnostic Considerations

Pregnant women seropositive for syphilis should be considered infected unless an adequate treatment history is clearly documented in the medical records and sequential serologic antibody titers have decreased as recommended for the syphilis stage. The risk for antepartum fetal infection or congenital syphilis at delivery is related to the syphilis stage during pregnancy, with the highest risk occurring during the primary and secondary stages. Quantitative maternal nontreponemal titer, especially if  $>1:8$ , might be a marker of early infection and bacteremia. However, risk for fetal infection is still substantial among pregnant women with late latent syphilis and low titers. Pregnant women with stable, serofast low nontreponemal titers who have previously been treated for syphilis might not require additional treatment; however, increasing or high antibody titers in a pregnant woman previously treated might indicate reinfection or treatment failure, and treatment should be offered.

If an automated treponemal test (e.g., EIA or CIA) is used for antepartum syphilis screening, all positive tests should be reflexed to a quantitative nontreponemal test (e.g., RPR or VDRL). If the nontreponemal test is negative, the results are considered discrepant and a second treponemal test (TP-PA is preferred) should be performed, preferably on the same specimen.

If the second treponemal test is positive (e.g., EIA positive, RPR negative, or TP-PA positive), current or previous syphilis infection can be confirmed. For women with a history of adequately treated syphilis who do not have ongoing risk, no further treatment is necessary. Women without a history of treatment should have the syphilis stage determined and should be treated accordingly with a recommended penicillin regimen.

If the second treponemal test is negative (e.g., EIA positive, RPR negative, or TP-PA negative), the positive EIA or CIA is more likely to represent a false-positive test result for women who are living in communities with low rates of syphilis, have a partner who is uninfected, and have no history of treated syphilis (637,638). If the woman is at low risk for syphilis, lacks signs or symptoms of primary syphilis, has a partner with no clinical or serologic evidence of syphilis, and is likely to follow up with clinical care, repeat serologic testing within 4 weeks can be considered to determine whether the EIA or CIA remains positive or if the RPR, VDRL, or TP-PA result becomes positive. If both the RPR and TP-PA remain negative, no further

treatment is necessary. If follow-up is not likely, women with an isolated reactive treponemal test and without a history of treated syphilis should be treated according to the syphilis stage.

## Treatment

Penicillin G is the only known effective antimicrobial for treating fetal infection and preventing congenital syphilis (639). Evidence is insufficient to determine the optimal penicillin regimen during pregnancy (640).

### Recommended Regimen for Syphilis During Pregnancy

Pregnant women should be treated with the recommended penicillin regimen for their stage of infection

## Other Management Considerations

The following recommendations should be considered for pregnant women with syphilis infection:

- Certain evidence indicates that additional therapy is beneficial for pregnant women to prevent congenital syphilis. For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered 1 week after the initial dose (641–643).
- When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis. However, this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (e.g., hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta) indicate a greater risk for fetal treatment failure (644); cases accompanied by these signs should be managed in consultation with obstetric specialists. A second dose of benzathine penicillin G 2.4 million units IM after the initial dose might be beneficial for fetal treatment in these situations.
- Women treated for syphilis during the second half of pregnancy are at risk for premature labor or fetal distress if the treatment precipitates the Jarisch-Herxheimer reaction (590). These women should be advised to seek obstetric attention after treatment if they notice any fever, contractions, or decrease in fetal movements. Stillbirth is a rare complication of treatment; however, concern for this complication should not delay necessary treatment. No data are available to support that corticosteroid treatment alters the risk for treatment-related complications during pregnancy.
- Missed doses  $>9$  days between doses are not acceptable for pregnant women receiving therapy for late latent syphilis (613). An optimal interval between doses is 7 days for pregnant women. If a pregnant woman does not return for the next dose on day 7, every effort should be made

to contact her and link her to immediate treatment within 2 days to avoid retreatment. Pregnant women who miss a dose of therapy should repeat the full course of therapy.

- All women who have syphilis should be offered testing for HIV at the time of diagnosis.

## Follow-Up

Coordinated prenatal care and treatment are vital because providers should document that women are adequately treated for the syphilis stage and ensure that the clinical and antibody responses are appropriate for the patient's disease stage. If syphilis is diagnosed and treated at or before 24 weeks' gestation, serologic titers should not be repeated before 8 weeks after treatment (e.g., at 32 weeks' gestation) but should be repeated again at delivery. Titers should be repeated sooner if reinfection or treatment failure is suspected. For syphilis diagnosed and treated after 24 weeks' gestation, serologic titers should be repeated at delivery.

A majority of women will not achieve a fourfold decrease in titers before delivery, although this does not indicate treatment failure (645). However, a fourfold increase in titer after treatment (e.g., from 1:8 to 1:32) that is sustained for >2 weeks is concerning for reinfection or treatment failure. Nontreponemal titers can increase immediately after treatment, presumably related to the treatment response. Therefore, unless symptoms and signs exist of primary or secondary syphilis, follow-up titer should not be repeated until approximately 8 weeks after treatment. Inadequate maternal treatment is likely if delivery occurs within 30 days of therapy, clinical signs of infection are present at delivery, or the maternal antibody titer at delivery is fourfold higher than the pretreatment titer.

## Management of Sex Partners

See Syphilis, Management of Sex Partners.

## Special Considerations

### Penicillin Allergy

No proven alternatives to penicillin are available for treatment of syphilis during pregnancy. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy).

Tetracycline and doxycycline are to be avoided in the second and third trimesters of pregnancy (431). Erythromycin and azithromycin should not be used because neither reliably cures maternal infection nor treats an infected fetus (640). Data are insufficient to recommend ceftriaxone or other cephalosporins

for treatment of maternal infection and prevention of congenital syphilis (646,647).

### HIV Infection

Placental inflammation from congenital syphilis infection might increase the risk for perinatal transmission of HIV. All women with HIV infection should be evaluated for syphilis and receive a penicillin regimen appropriate for the syphilis stage. Data are insufficient to recommend any alternative regimens for pregnant women with syphilis and HIV infection (see Syphilis Among Persons with HIV).

## Congenital Syphilis

The rate of reported congenital syphilis in the United States has increased dramatically since 2012. During 2019, a total of 1,870 cases of congenital syphilis were reported, including 94 stillbirths and 34 infant deaths (141). The 2019 national rate of 48.5 cases per 100,000 live births represents a 41% increase relative to 2018 (34.3 cases per 100,000 live births) and a 477% increase relative to 2012 (8.4 cases per 100,000 live births). During 2015–2019, the rate of congenital syphilis increased 291.1% (12.4 to 48.5 per 100,000 live births), which mirrors increases in the rate of primary and secondary syphilis among females aged 15–44 years (a 171.9% increase, from 3.2 to 8.7 per 100,000 females).

Effective prevention and detection of congenital syphilis depend on identifying syphilis among pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit and at 28 weeks' gestation and at delivery for women who live in communities with high rates of syphilis, women with HIV infection, or those who are at increased risk for syphilis acquisition. Certain states have recommended screening three times during pregnancy for all women; clinicians should screen according to their state's guidelines.

Maternal risk factors for syphilis during pregnancy include sex with multiple partners, sex in conjunction with drug use or transactional sex, late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care, methamphetamine or heroin use, incarceration of the woman or her partner, and unstable housing or homelessness (174,633–636). Moreover, as part of the management of pregnant women who have syphilis, providers should obtain information concerning ongoing risk behaviors and treatment of sex partners to assess the risk for reinfection.

Routine screening of neonatal sera or umbilical cord blood is not recommended because diagnosis at that time does not prevent congenital syphilis in certain newborns. No mother or newborn infant should leave the hospital without maternal

serologic status having been documented at least once during pregnancy. Any woman who had no prenatal care before delivery or is considered at increased risk for syphilis acquisition during pregnancy should have the results of a syphilis serologic test documented before she or her neonate is discharged. A quantitative RPR is needed at the time of delivery to compare with the neonate's nontreponemal test result. If a stat RPR is unavailable and a rapid treponemal test is performed at delivery, the results should be confirmed by using standard syphilis serologic laboratory tests (e.g., RPR and treponemal test) and algorithms.

## Evaluation and Treatment of Neonates

Diagnosis of congenital syphilis can be difficult because maternal nontreponemal and treponemal immunoglobulin G (IgG) antibodies can be transferred through the placenta to the fetus, complicating the interpretation of reactive serologic tests for syphilis among neonates (infants aged <30 days). Therefore, treatment decisions frequently must be made on the basis of identification of syphilis in the mother; adequacy of maternal treatment; presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate; and comparison of maternal (at delivery) and neonatal nontreponemal serologic titers (e.g., RPR or VDRL) by using the same test, preferably conducted by the same laboratory. Any neonate at risk for congenital syphilis should receive a full evaluation and testing for HIV.

All neonates born to mothers who have reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal serologic test (RPR or VDRL) performed on the neonate's serum because umbilical cord blood can become contaminated with maternal blood and yield a false-positive result, and Wharton's jelly within the umbilical cord can yield a false-negative result. The nontreponemal test performed on the neonate should be the same type of nontreponemal test performed on the mother.

Conducting a treponemal test (e.g., TP-PA, immunoassay-EIA, CIA, or microbead immunoassay) on neonatal serum is not recommended because it is difficult to interpret, as passively transferred maternal antibodies can persist for >15 months. Commercially available IgM tests are not recommended.

All neonates born to women who have reactive nontreponemal serologic tests for syphilis at delivery should be examined thoroughly for evidence of congenital syphilis (e.g., nonimmune hydrops, conjugated or direct hyperbilirubinemia<sup>†</sup> or cholestatic jaundice or cholestasis, hepatosplenomegaly, rhinitis, skin rash, or pseudoparalysis of an extremity). Pathologic examination of the placenta or umbilical cord using specific staining (e.g., silver) or a *T. pallidum* PCR test using

a CLIA-validated test should be considered; direct fluorescence antibody (DFA-TP) reagents are unavailable (565). Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash or nasal discharge) also should be performed. In addition to these tests, for stillborn infants, skeletal survey demonstrating typical osseous lesions might aid in the diagnosis of congenital syphilis because these abnormalities are not detected on fetal ultrasound.

The following scenarios describe the recommended congenital syphilis evaluation and treatment of neonates born to women who had reactive nontreponemal and treponemal serologic tests for syphilis during pregnancy (e.g., RPR reactive, TP-PA reactive or EIA reactive, RPR reactive) and have a reactive nontreponemal test at delivery (e.g., RPR reactive). Maternal history of infection with *T. pallidum* and treatment for syphilis should be considered when evaluating and treating the neonate for congenital syphilis in most scenarios, except when congenital syphilis is proven or highly probable.

### Scenario 1: Confirmed Proven or Highly Probable Congenital Syphilis

Any neonate with

- an abnormal physical examination that is consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold<sup>§</sup> (or greater) higher than the mother's titer at delivery (e.g., maternal titer = 1:2, neonatal titer ≥1:8 or maternal titer = 1:8, neonatal titer ≥1:32)<sup>¶</sup>; or
- a positive darkfield test or PCR of placenta, cord, lesions, or body fluids or a positive silver stain of the placenta or cord.

### Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein\*\*

<sup>§</sup> One dilution is within the test performance of nontreponemal tests and is not a significant change.

<sup>¶</sup> The absence of a fourfold or greater titer for a neonate does not exclude congenital syphilis.

\*\* Interpretation of CSF test results requires a nontraumatic lumbar puncture (i.e., a CSF sample that is not contaminated with blood). CSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age and are higher among preterm infants. Studies indicate that 95% of healthy neonates have values of ≤16–19 WBCs/mm<sup>3</sup> or protein levels of ≤115–118 mg/dL on CSF examination. During the second month of life, 95% of healthy infants have ≤9–11 WBCs/mm<sup>3</sup> or protein levels of ≤89–91 mg/dL. Lower values (i.e., 5 WBCs/mm<sup>3</sup> and protein level of 40 mg/dL) might be considered the upper limits of normal for older infants. Other causes of elevated values should be considered when an infant is being evaluated for congenital syphilis (**Sources:** Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. Pediatrics 2010;125:257–64; Shah SS, Ebberson J, Kestenbaum LA, Hodinka RL, Zorc JJ. Age-specific reference values for cerebrospinal fluid protein concentration in neonates and young infants. J Hosp Med 2011;6:22–7; Thomson J, Sucharew H, Cruz AT, et al.; Pediatric Emergency Medicine Collaborative Research Committee [PEM CRC] HSV Study Group. Cerebrospinal fluid reference values for young infants undergoing lumbar puncture. Pediatrics 2018;141:e20173405.)

<sup>†</sup> Direct hyperbilirubinemia is direct bilirubin level >2 mg/dL (34 umol/L) or 20% of the total bilirubin level.

- Complete blood count (CBC) and differential and platelet count
- Long-bone radiographs
- Other tests as clinically indicated (e.g., chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response)

#### **Recommended Regimens, Confirmed or Highly Probable Congenital Syphilis**

**Aqueous crystalline penicillin G** 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days  
*or*

**Procaine penicillin G** 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

#### **Recommended Regimens, Possible Congenital Syphilis**

**Aqueous crystalline penicillin G** 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

*or*

**Procaine penicillin G** 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

*or*

**Benzathine penicillin G** 50,000 units/kg body weight/dose IM in a single dose

Before using the single-dose benzathine penicillin G regimen, the recommended evaluation (i.e., CSF examination, long-bone radiographs, and CBC with platelets) should be normal, and follow-up should be certain. If any part of the neonate's evaluation is abnormal or not performed, if the CSF analysis is uninterpretable because of contamination with blood, or if follow-up is uncertain, a 10-day course of penicillin G is required.

If the neonate's nontreponemal test is nonreactive and the provider determines that the mother's risk for untreated syphilis is low, treatment of the neonate with a single IM dose of benzathine penicillin G 50,000 units/kg body weight for possible incubating syphilis can be considered without an evaluation. Neonates born to mothers with untreated early syphilis at the time of delivery are at increased risk for congenital syphilis, and the 10-day course of penicillin G should be considered even if the neonate's nontreponemal test is nonreactive, the complete evaluation is normal, and follow-up is certain.

#### **Scenario 2: Possible Congenital Syphilis**

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and one of the following:

- The mother was not treated, was inadequately treated, or has no documentation of having received treatment.
- The mother was treated with erythromycin or a regimen other than those recommended in these guidelines (i.e., a nonpenicillin G regimen).††
- The mother received the recommended regimen but treatment was initiated <30 days before delivery.

#### **Recommended Evaluation**

- CSF analysis for VDRL, cell count, and protein\*\*
- CBC, differential, and platelet count
- Long-bone radiographs

This evaluation is not necessary if a 10-day course of parenteral therapy is administered, although such evaluations might be useful. For instance, a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC, platelet count, and long-bone radiographs) can be performed to further support a diagnosis of congenital syphilis.

†† A women treated with a regimen other than recommended in these guidelines should be considered untreated.

#### **Scenario 3: Congenital Syphilis Less Likely**

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal or less than fourfold of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and both of the following are true:

- The mother was treated during pregnancy, treatment was appropriate for the infection stage, and the treatment regimen was initiated ≥30 days before delivery.
- The mother has no evidence of reinfection or relapse.

#### **Recommended Evaluation**

No evaluation is recommended.

#### **Recommended Regimen, Congenital Syphilis Less Likely**

**Benzathine penicillin G** 50,000 units/kg body weight/dose IM in a single dose\*

\* Another approach involves not treating the newborn if follow-up is certain but providing close serologic follow-up every 2–3 months for 6 months for infants whose mothers' nontreponemal titers decreased at least fourfold after therapy for early syphilis or remained stable for low-titer, latent syphilis (e.g., VDRL <1:2 or RPR <1:4).

## Scenario 4: Congenital Syphilis Unlikely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold of the maternal titer at delivery<sup>§</sup> and both of the following are true:

- The mother's treatment was adequate before pregnancy.
- The mother's nontreponemal serologic titer remained low and stable (i.e., serofast) before and during pregnancy and at delivery (e.g., VDRL ≤1:2 or RPR ≤1:4).

### Recommended Evaluation

No evaluation is recommended.

#### Recommended Regimen, Congenital Syphilis Unlikely

No treatment is required. However, any neonate with reactive nontreponemal tests should be followed serologically to ensure the nontreponemal test returns to negative (see Follow-Up). Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test.

The following situations describe management of neonates born to women screened during pregnancy by using the reverse sequence algorithm with reactive treponemal serologic tests and a nonreactive nontreponemal serologic test.

**Reactive maternal treponemal serologies with a nonreactive nontreponemal serology (e.g., EIA reactive, RPR nonreactive, or TP-PA reactive) during pregnancy.** Syphilis is highly unlikely for neonates born to mothers with a nonreactive nontreponemal test after adequate treatment for syphilis during pregnancy or documentation of adequate treatment before pregnancy (with no evidence of reinfection or relapse). If testing is performed again at delivery and 1) the maternal nontreponemal test remains nonreactive and 2) the neonate has a normal physical examination and nonreactive nontreponemal test (e.g., RPR nonreactive), the provider should consider managing similarly to Scenario 4 without a laboratory evaluation and with no treatment required. Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered if syphilis exposure is possible within 1 month of delivery and follow-up of the mother and infant is uncertain.

**Isolated reactive maternal treponemal serology (e.g., EIA reactive, RPR nonreactive, or TP-PA nonreactive) during pregnancy.** Syphilis is unlikely for neonates born to mothers screened with the reverse sequence algorithm with isolated reactive maternal treponemal serology. Among low-prevalence populations, these are likely false-positive results and might become nonreactive with repeat testing (638). If these neonates have a normal physical examination and the risk for syphilis is low in the mother, no evaluation and treatment are

recommended for the neonate. If syphilis exposure is possible or unknown in the mother or the mother desires further evaluation to definitively rule out syphilis, repeat serology within 4 weeks is recommended to evaluate for early infection (see Syphilis During Pregnancy).

**Isolated reactive maternal treponemal serology (e.g., rapid treponemal test) at delivery.** For mothers with late or no prenatal care with a reactive rapid treponemal test at delivery, confirmatory laboratory-based testing should be performed; however, results should not delay evaluation and treatment of the neonate. These neonates should be evaluated and treated with a 10-day course of penicillin as recommended in Scenario 1, and consultation with a specialist is recommended.

### Follow-Up

All neonates with reactive nontreponemal tests should receive thorough follow-up examinations and serologic testing (i.e., RPR or VDRL) every 2–3 months until the test becomes nonreactive.

For a neonate who was not treated because congenital syphilis was considered less likely or unlikely, nontreponemal antibody titers should decrease by age 3 months and be nonreactive by age 6 months, indicating that the reactive test result was caused by passive transfer of maternal IgG antibody. At age 6 months, if the nontreponemal test is nonreactive, no further evaluation or treatment is needed; if the nontreponemal test is still reactive, the infant is likely infected and should be treated.

Treated neonates who exhibit persistent nontreponemal test titers by age 6–12 months should be reevaluated through CSF examination and managed in consultation with an expert. Retreatment with a 10-day course of a penicillin G regimen might be indicated.

Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be retested at age 3 months to rule out serologically negative incubating congenital syphilis at the time of birth. Treponemal tests should not be used to evaluate treatment response because the results are qualitative, and passive transfer of maternal IgG treponemal antibody might persist for >15 months.

Neonates whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless they exhibit persistent nontreponemal serologic test titers at age 6–12 months. Persistent nontreponemal titers and CSF abnormalities should be managed in consultation with an expert.

### Special Considerations

#### Penicillin Allergy

Neonates who require treatment for congenital syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should

be desensitized and then treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy). Skin testing remains unavailable for neonates because the procedure has not been standardized for this age group. Data are insufficient regarding use of other antimicrobial agents (e.g., ceftriaxone) for congenital syphilis among neonates. If a nonpenicillin G agent is used, close clinical and serologic follow-up is required in consultation with an expert. Repeat CSF examination should be performed if the initial CSF examination was abnormal.

### Penicillin Shortage

During periods when the availability of aqueous crystalline penicillin G is compromised, the following is recommended (<https://www.cdc.gov/std/treatment/drug-notices.htm>):

- For neonates with clinical evidence of congenital syphilis (see Scenario 1), check local sources for aqueous crystalline penicillin G (potassium or sodium) and notify CDC and FDA of limited supply. If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 units/kg body weight/dose IM/day in a single daily dose for 10 days).
- If aqueous or procaine penicillin G is unavailable, ceftriaxone (50–75 mg/kg body weight/day IV every 24 hours) can be considered with thorough clinical and serologic follow-up and in consultation with an expert because evidence is insufficient to support using ceftriaxone for treating congenital syphilis. Ceftriaxone should be used with caution in neonates with jaundice.
- For neonates without any clinical evidence of congenital syphilis (see Scenario 2 and Scenario 3), use
  - procaine penicillin G 50,000 units/kg body weight/dose/day IM in a single dose for 10 days, or
  - benzathine penicillin G 50,000 units/kg body weight IM as a single dose.
- If any part of the evaluation for congenital syphilis is abnormal or was not performed, CSF examination is not interpretable, or follow-up is uncertain, procaine penicillin G is recommended. A single dose of ceftriaxone is inadequate therapy.
- For premature neonates who have no clinical evidence of congenital syphilis (see Scenario 2 and Scenario 3) and might not tolerate IM injections because of decreased muscle mass, IV ceftriaxone can be considered with thorough clinical and serologic follow-up and in consultation with an expert. Ceftriaxone dosing should be adjusted according to birthweight.

### HIV Infection

Evidence is insufficient to determine whether neonates who have congenital syphilis and HIV infection or whose mothers have HIV require different therapy or clinical management than is recommended for all neonates. All neonates with congenital syphilis should be managed similarly, regardless of HIV status.

### Evaluation and Treatment of Infants and Children with Congenital Syphilis

Infants and children aged ≥1 month who are identified as having reactive serologic tests for syphilis (e.g., RPR reactive, TP-PA reactive or EIA reactive, RPR reactive) should be examined thoroughly and have maternal serology and records reviewed to assess whether they have congenital or acquired syphilis (see Primary and Secondary Syphilis; Latent Syphilis; Sexual Assault or Abuse of Children). In the case of extremely early or incubating syphilis at the time of delivery, all maternal serologic tests might have been negative; thus, infection might be undetected until a diagnosis is made later in the infant or child. Any infant or child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

International adoptee, immigrant, or refugee children from countries where treponemal infections (e.g., yaws or pinta) are endemic might have reactive nontreponemal and treponemal serologic tests, which cannot distinguish between syphilis and other subspecies of *T. pallidum* (651). These children might also have syphilis (*T. pallidum* subspecies *pallidum*) and should be evaluated for congenital syphilis.

### Recommended Evaluation

The following evaluations should be performed:

- CSF analysis for VDRL, cell count, and protein
- CBC, differential, and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, abdominal ultrasound, ophthalmologic examination, neuroimaging, and auditory brain-stem response)

### Recommended Regimen for Congenital Syphilis Among Infants and Children

**Aqueous crystalline penicillin G** 200,000–300,000 units/kg body weight/day IV, administered as 50,000 units/kg body weight every 4–6 hours for 10 days

If the infant or child has no clinical manifestations of congenital syphilis and the evaluation (including the CSF examination) is normal, treatment with <3 weekly doses of benzathine penicillin G 50,000 units/kg body weight IM can be considered. A single dose of benzathine penicillin G 50,000 units/kg body weight IM up to the adult dose of

2.4 million units in a single dose can be considered after the 10-day course of IV aqueous penicillin G to provide more comparable duration for treatment in those who have no clinical manifestations and normal CSF. All of these treatment regimens should also be adequate for children who might have other treponemal infections.

## Follow-Up

Thorough follow-up examinations and serologic testing (i.e., RPR or VDRL) of infants and children treated for congenital syphilis after the neonatal period (aged >30 days) should be performed every 3 months until the test becomes nonreactive or the titer has decreased fourfold. The serologic response after therapy might be slower for infants and children than neonates. If these titers increase at any point >2 weeks or do not decrease fourfold after 12–18 months, the infant or child should be evaluated (e.g., CSF examination), treated with a 10-day course of parenteral penicillin G, and managed in consultation with an expert. Treponemal tests (e.g., EIA, CIA, or TP-PA) should not be used to evaluate treatment response because the results are qualitative and persist after treatment, and passive transfer of maternal IgG treponemal antibody might persist for >15 months after delivery. Infants or children whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless their serologic titers do not decrease fourfold after 12–18 months. After 18 months of follow-up, abnormal CSF indices that persist and cannot be attributed to other ongoing illness indicate that retreatment is needed for possible neurosyphilis and should be managed in consultation with an expert.

## Special Considerations

### *Penicillin Allergy*

Infants and children who require treatment for congenital syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized and treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy). Skin testing remains unavailable for infants and children because the procedure has not been standardized for this age group. Data are insufficient regarding use of other antimicrobial agents (e.g., ceftriaxone) for congenital syphilis among infants and children. If a nonpenicillin G agent is used, close clinical, serologic, and CSF follow-up is required in consultation with an expert.

### *Penicillin Shortage*

During periods when availability of penicillin G is compromised, management options are similar to options for the neonate (see Evaluation and Treatment of Neonates).

- For infants and children with clinical evidence of congenital syphilis, if IV penicillin is limited after checking local sources and notifying CDC and FDA about limited supplies, procaine penicillin G (50,000 units/kg body weight/dose IM up to the adult dose of 2.4 million units a day in a single daily dose for 10 days) is recommended.
- If procaine penicillin G is not available, ceftriaxone (in doses for age and weight) can be considered with thorough clinical and serologic follow-up. Infants and children receiving ceftriaxone should be managed in consultation with an expert because evidence is insufficient to support use of ceftriaxone for treatment of congenital syphilis among infants or children. For infants aged ≥30 days, use ceftriaxone 75 mg/kg body weight/day IV or IM in a single daily dose for 10–14 days (dose adjustment might be necessary on the basis of current weight). For children, ceftriaxone 100 mg/kg body weight/day in a single daily dose is recommended.
- For infants and children without any clinical evidence of infection (see Scenario 2 and Scenario 3), use
  - procaine penicillin G 50,000 units/kg body weight/dose IM up to the adult dose of 2.4 million units a day in a single dose for 10 days, or
  - benzathine penicillin G 50,000 units/kg body weight IM up to the adult dose of 2.4 million units as a single dose.
- If any part of the evaluation for congenital syphilis is abnormal or not performed, CSF examination is not interpretable, or follow-up is uncertain, procaine penicillin G is recommended. In these scenarios, a single dose of ceftriaxone is inadequate therapy.

### *HIV Infection*

Evidence is insufficient to determine whether infants and children who have congenital syphilis and HIV infection or whose mothers have HIV require different therapy or clinical management than what is recommended for all infants and children. All infants and children with congenital syphilis should be managed similarly, regardless of HIV status.

## Management of Persons Who Have a History of Penicillin Allergy

Penicillin and other  $\beta$ -lactam antibiotics have a crucial role in treating STIs. Penicillin is recommended for all clinical stages of syphilis, and no proven alternatives exist for treating neurosyphilis, congenital syphilis, or syphilis during pregnancy. Ceftriaxone, a third-generation cephalosporin, is recommended for gonorrhea treatment. For extragenital site infections, especially pharyngeal, failure rates of nonceftriaxone

regimens can be substantial. In most clinical settings, patients who report a penicillin allergy are not treated with  $\beta$ -lactam antimicrobials. For patients with a diagnosis of gonorrhea and a concomitant reported allergy to penicillin, ceftriaxone is often avoided, even though the cross-reactivity between penicillin allergy and third-generation cephalosporins is low (652–654).

Prevalence of reported allergy to penicillin is approximately 10% among the U.S. population and higher among hospital inpatients and residents in health care-related facilities (655–658). One large study in an STI clinic revealed that 8.3% of patients reported penicillin or another  $\beta$ -lactam antibiotic allergy (659). Penicillin allergy is often overreported, with the majority of patients who report penicillin allergy able to tolerate the medication (660). The prevalence of reported penicillin allergy in low-income countries is unknown; however, limited data indicate that penicillin is one of the most frequently reported antibiotic allergies (661).

Patients often are incorrectly labeled as allergic to penicillin and are therefore denied the benefit of a  $\beta$ -lactam therapy. The presence of a penicillin allergy label considerably reduces prescribing options for affected patients. Moreover, penicillin allergy labels lead to the use of more expensive and less effective drugs and can result in adverse consequences, including longer length of hospital stay and increased risk for infection. Multiple studies have described that persons with reported penicillin or another  $\beta$ -lactam antibiotic allergy have higher rates of surgical-site infections, methicillin-resistant *Staphylococcus aureus* infections, and higher medical care usage (653,662–664).

The overreported prevalence of penicillin allergy is secondary to imprecise use of the term “allergy” by families and clinicians and lack of clarity to differentiate between immunoglobulin E (IgE)-mediated hypersensitivity reactions, drug intolerances, and other idiosyncratic reactions that can occur days after exposure. Approximately 80% of patients with a true IgE-mediated allergic reaction to penicillin have lost the sensitivity after 10 years (658). Thus, patients with recent reactions are more likely to be allergic than patients with remote reactions, and patients who had allergic reactions in the distant past might no longer be reactive.

In a Baltimore, Maryland, STI clinic study, only 7.1% of the patients who reported allergy to penicillin or to another  $\beta$ -lactam antibiotic had an objective positive test for penicillin allergy (659). Moreover, in studies that have incorporated penicillin skin testing and graded oral challenge among persons with reported penicillin allergy, the true rates of allergy are low, ranging from 1.5% to 6.1% (665–667). Studies in preoperative surgical patients with reported penicillin allergy, evaluated for cardiovascular surgery (668) or orthopedics (669), have rates of skin test positivity <8.5%. However, when patients with high-risk penicillin allergy histories are excluded, 99%

of patients could receive  $\beta$ -lactams. In hospitalized patients and other populations with comorbidities, the typical rates of validated penicillin allergy among patients who report a history of penicillin allergy are 2.5%–9.0% (670–673).

## Cross-Reactivity with Cephalosporins

Penicillin and cephalosporins both contain a  $\beta$ -lactam ring. This structural similarity has led to considerable confusion regarding cross-reactivity of these drugs and the risks for allergic reactions from cephalosporins among penicillin-allergic patients. In most clinical settings, patients with reported penicillin allergy are precluded from treatment with such cephalosporin antibiotics as ceftriaxone. Third-generation cephalosporins (e.g., ceftriaxone and cefixime) have lower cross-reactivity with IgE-mediated penicillin-allergic patients (<1%) compared with first- and second-generation cephalosporins (range: 1%–8%). Moreover, anaphylaxis secondary to cephalosporins is extremely rare among persons who report a penicillin allergy and is estimated to occur at a rate of one per 52,000 persons (652). Data from the Kaiser health care system reported that among 3,313 patients with self-reported cephalosporin allergy who received a cephalosporin (mostly first generation), no cases of anaphylaxis were reported (652). Use of third- and fourth-generation cephalosporins and carbapenems is safe for patients without a history of any IgE-mediated symptoms (e.g., anaphylaxis or urticaria) from penicillin during the preceding 10 years.

## Validating Penicillin or Another $\beta$ -Lactam Antibiotic Allergy

Evaluating a patient who reports a penicillin or another  $\beta$ -lactam antibiotic allergy involves three steps: 1) obtaining a thorough medical history, including previous exposures to penicillin or other  $\beta$ -lactam antibiotics (658); 2) performing a skin test evaluation by using the penicillin major and minor determinants; and 3) among those who have a negative penicillin skin test, performing an observed oral challenge with 250 mg amoxicillin before proceeding directly to treatment with the indicated  $\beta$ -lactam therapy (667,675).

For persons who have a positive skin test reactive to penicillin (either to the major or minor determinants), treatment with a  $\beta$ -lactam antibiotic is not usually advised, and other effective antimicrobials should be used (656,658). For persons among whom the only therapy option is a penicillin antibiotic (e.g., a patient with neurosyphilis or a pregnant woman with syphilis) and among whom a penicillin skin test is positive, induction of penicillin tolerance (also referred to as desensitization) is required (675). Desensitization protocols to penicillin should

be performed by allergists, and they require a monitored inpatient environment.

## Penicillin Skin Testing

Penicillin skin testing with a major determinant analog (penicilloyl-polylysine) and minor determinants (benzylpenicilloate, benzylpenilloate, or benzylpenicillin isomers of penicillin) are used for skin test evaluation for IgE-dependent penicillin allergy and can reliably identify persons at high risk for IgE-mediated reactions to penicillin (658,660,676). Until recently, penicillin skin testing in the United States only included the major determinant benzyl penicillin poly-L-lysine (Pre-Pen) in addition to penicillin G. This test identifies approximately 90%–99% of the IgE-mediated penicillin-allergic patients. Because the remaining 1%–10% of penicillin-allergic patients who are not captured by this penicillin skin test are due to minor determinants IgE antibodies, the standard practice is to follow skin testing with an observed oral challenge of amoxicillin 250 mg with 1 hour of observation. If the skin test and oral challenge are both negative, the risk for IgE-mediated anaphylaxis approaches zero and is equivalent to that of a person who has never reported an allergy to penicillin.

A revised version of the penicillin skin test kit, which includes the major determinant reagent Pre-Pen, minor determinants, and amoxicillin, is being evaluated by FDA. This penicillin skin test kit has been evaluated among 455 patients (677) with previous allergy history and has a negative predictive value of 98%. If approved, this kit might eliminate the need for oral challenge.

Penicillin skin testing has become a clinically significant element in antibiotic stewardship programs, and the procedure has been increasingly used by hospital-based pharmacists, hospitalists, and infectious disease physicians (670,672,673,678,679) as part of overall antibiotic stewardship interventions. When integrated into stewardship, the rates of  $\beta$ -lactam antibiotic use increased substantially (670).

## Recommendations

Persons with a history of severe adverse cutaneous reaction (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis) and other severe non-IgE-mediated reactions (e.g., interstitial nephritis or hemolytic anemia) are not candidates for penicillin skin testing or challenge. Penicillin and any other  $\beta$ -lactam antibiotics should be avoided indefinitely among these patients, who should be referred to an allergy center for further evaluation. Similarly, patients who deny penicillin allergy, but who report previous IgE-type reactions to cephalosporins, should be referred to an allergist for specific cephalosporin testing.

In a time of increasing antimicrobial resistance, following recommended use of antibiotic treatments is crucial. STI programs and clinicians should promote increased access to penicillin allergy testing. Allergy testing is being provided by clinicians in primary care and hospital settings. If appropriate, STI programs and ambulatory settings should consider developing expanded access to penicillin or  $\beta$ -lactam allergy assessment.

Persons with high-risk symptom histories (e.g., anaphylaxis within the previous 10 years) should not be administered penicillin or a  $\beta$ -lactam antibiotic in an ambulatory setting. Furthermore, these persons with high-risk symptoms should not receive penicillin skin testing or amoxicillin oral challenge in an ambulatory STI setting and should be referred to an allergist for further evaluation.

High-risk symptom histories include development of the following after penicillin or  $\beta$ -lactam administration: anaphylaxis within 6 hours or severe adverse cutaneous reaction (e.g., eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, or acute generalized exanthematous pustulosis) and other severe non-IgE-mediated reactions (e.g., kidney or hepatic injury, hemolytic anemia, or thrombocytopenia).

## Direct Treatment Approach for Ceftriaxone

Among persons with confirmed IgE-mediated penicillin allergy, the level of cross-reactivity with third-generation cephalosporins is low (652,680,681). If a patient has a low-risk history for an IgE-mediated penicillin allergy, ambulatory settings often treat with third-generation cephalosporins without further testing. Low-risk history includes one nonspecific symptom (e.g., gastrointestinal intolerance, headache, fatigue, or nonurticarial rash) (Box 2). In addition, a family history of penicillin or  $\beta$ -lactam allergy alone is not a contraindication for treatment with  $\beta$ -lactam antibiotics. This practice is increasingly being used in ambulatory settings and for preoperative prophylaxis (658,663,680,682–684).

### BOX 2. Low-risk history in patients who report penicillin allergy

#### Gastrointestinal symptoms

- Headache
- Pruritis without rash
- Localized rash
- Delayed onset rash (>24 hours)
- Symptoms unknown
- Family history of penicillin or another drug allergy
- Patient denies allergy but it is on the medical record

## Patients at Low Risk for Oral Challenge

If the patient gives only a low-risk history of IgE-mediated penicillin allergy that includes symptoms such as gastrointestinal intolerance, headache, fatigue, or nonspecific pruritus, or gives a family history only, an oral challenge can be administered to document the absence of allergy (Box 2). If the reaction occurred in the distant past (>10 years), the likelihood is reduced even further (653,658,663,682,683,685,686). The risk for severe amoxicillin-mediated anaphylaxis has decreased over time and is rare. In the United Kingdom during 1972–2007, one fatal case of amoxicillin-mediated anaphylaxis was reported (684).

## Skin Testing for Penicillin Allergy

Skin testing for penicillin allergy should be performed if any indication exists that the symptoms were secondary to an IgE-mediated hypersensitivity. Testing is also indicated as a potential diagnostic procedure to definitively rule out penicillin allergy and document a negative allergy status in the medical record (i.e., delabeling). Because penicillin allergy testing does not test for multiple minor determinants, a person with a negative skin test should follow up with an oral challenge to confirm the negative status.

Persons with negative results of a penicillin skin test, followed by an amoxicillin oral challenge, can receive conventional penicillin therapy safely if needed. Persons with positive skin test results and for whom no other clinical options exist (e.g., neurosyphilis and syphilis in a pregnant woman) should be referred to an allergist and desensitized before initiating treatment.

## Testing Procedures

Penicillin skin testing includes use of skin test reagents for identifying persons at risk for adverse reactions (Box 3), followed by initial pinprick screening with penicillin major determinants (Pre-Pen) and penicillin G, followed by intradermal testing if pinprick results are negative. Penicillin testing procedures are performed in accordance with the Pre-Pen test kit instructions (<https://penallergytest.com/wp-content/uploads/PRE-PEN-Package-Insert.pdf>). Saline negative controls and histamine positive controls are an integral part of the procedure. Penicillin skin testing should not be performed for patients who have taken antihistamines within the past 7 days.

Skin testing can be safely performed by trained nonallergists and has been implemented as an antimicrobial stewardship intervention by internal medicine physicians, pharmacists, hospitalists, and infectious disease physicians (670,673,678,679). Patients tested should also receive documentation of status, and the results should be entered in the medical record.

Penicillin skin testing during pregnancy is considered safe. For pregnant persons who report a penicillin or  $\beta$ -lactam allergy, penicillin allergy is an important consideration in treating syphilis during pregnancy and the potential for group B streptococcal infection and preoperative prophylaxis if a cesarean delivery is required. However, oral challenges should not be performed unless in a setting where additional support services are available.

## Managing Persons Being Tested

Patients who have a positive skin test should not receive  $\beta$ -lactam drugs in the ambulatory setting and should be referred to an allergist or penicillin allergy expert for further evaluation. The allergy testing results should be documented in the medical record. Patients who test negative should be informed that their risk for anaphylaxis is extremely low and is equivalent to a person who does not report an allergy history. If treatment with penicillin or ceftriaxone is indicated, it can be administered safely. Documentation of testing results should be provided to the patient.

## Desensitization

Desensitization is required for persons who have a documented penicillin allergy and for whom no therapeutic alternatives exist (e.g., syphilis during pregnancy and persons with neurosyphilis). Modified protocols might be considered

### BOX 3. Skin test reagents for identifying persons at risk for adverse reactions to penicillin

#### Major determinant

- Benzylpenicilloyl polylysine injection (Pre-Pen) (AllerQuest) ( $6 \times 10^{-5}$ M)

#### Minor determinant precursors

- Benzylpenicillin G ( $10^{-2}$ M, 3.3 mg/mL, 10,000 units/mL)
- Benzylpenicilloate ( $10^{-2}$ M, 3.3 mg/mL)
- Benzylpenicilloate (or penicilloyl propylamine) ( $10^{-2}$ M, 3.3 mg/mL)

**Aged penicillin is not an adequate source of minor determinants. Penicillin G should either be freshly prepared or come from a fresh-frozen source.**

#### Positive control

- Commercial histamine for scratch testing (1.0 mg/mL)

#### Negative control

- Diluent (usually saline) or allergen diluent

**Source:** Adapted from Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987;107:204–15.

on the basis of the clinical syndrome, drug of choice, and route of administration (687–690). Patients might require referral to a specialty center where desensitization can be performed.

## Allergy Referral Resources

With increased access to skin testing kits and the need to better target therapy for gonorrhea and syphilis, programs should identify local allergy consultant resources.

# Diseases Characterized by Urethritis and Cervicitis

## Urethritis

Urethritis, as characterized by urethral inflammation, can result from either infectious or noninfectious conditions. Symptoms, if present, include dysuria, urethral pruritis, and mucoid, mucopurulent, or purulent discharge. Signs of urethral discharge on examination can also be present among persons without symptoms. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *M. genitalium* has been strongly associated with urethritis and, less commonly, prostatitis (691–697). If POC diagnostic tools (e.g., Gram, methylene blue [MB], or gentian violet [GV] stain microscopy) are unavailable, drug regimens effective against both gonorrhea and chlamydia should be administered. Further testing to determine the specific etiology is recommended for preventing complications, reinfection, and transmission because a specific diagnosis might improve treatment compliance, delivery of risk-reduction interventions, and partner services. Both chlamydia and gonorrhea are reportable to health departments. NAATs are preferred for detecting *C. trachomatis* and *N. gonorrhoeae*, and urine is the preferred specimen for males (553). NAAT-based tests for diagnosing *T. vaginalis* among men with urethritis have not been cleared by FDA; however, laboratories have performed the CLIA-compliant validation studies (698) needed to provide such testing.

## Etiology

Multiple organisms can cause infectious urethritis. The presence of gram-negative intracellular diplococci (GNID) or purple intracellular diplococci (MB or GV) on urethral smear is indicative of presumed gonococcal infection, which is frequently accompanied by chlamydial infection. Nongonococcal urethritis (NGU), which is diagnosed when microscopy of urethral secretions indicate inflammation without GNID or MB or GV purple intracellular diplococci, is caused by *C. trachomatis* in 15%–40% of cases; however,

prevalence varies by age group, with a lower proportion of disease occurring among older men (699). Documentation of chlamydial infection as NGU etiology is essential because of the need for partner referral for evaluation and treatment to prevent complications of chlamydia, especially for female partners. Complications of *C. trachomatis*-associated NGU among males include epididymitis, prostatitis, and reactive arthritis.

*M. genitalium* is associated with symptoms of urethritis and urethral inflammation and accounts for 15%–25% of NGU cases in the United States (691–693,696,697,700). Among men with symptoms of urethritis, *M. genitalium* was detected in 11% of those with urethritis in Australia (701), 12%–15% in the United Kingdom (702–704), 15% in South Africa (696), 19% in China (705), 21% in Korea, 22% in Japan (706), and 28.7% in the United States (range: 20.4%–38.8%) (697). Data are inconsistent regarding other *Mycoplasma* and *Ureaplasma* species as etiologic agents of urethritis (707). The majority of men with *Ureaplasma* infections do not have overt disease unless a high organism load is present.

*T. vaginalis* can cause urethritis among heterosexual men; however, the prevalence varies substantially by U.S. geographic region, age, and sexual behavior and within specific populations. Studies among men with and without overt urethritis in developed countries document relatively low rates of *T. vaginalis* in the Netherlands (0.5%) (708), Japan (1.3%) (706,709), the United States (2.4%) (710), and the United Kingdom (3.6%) (703). Studies in other countries have documented higher rates, such as in Croatia (8.2%) (711) and Zimbabwe (8.4%) (712), particularly among symptomatic patients.

*Neisseria meningitidis* can colonize mucosal surfaces and cause urethritis (713). Urogenital *N. meningitidis* rates and duration of carriage, prevalence of asymptomatic and symptomatic infection, and modes of transmission have not been systematically described; however, studies indicate that *N. meningitidis* can be transmitted through oral-penile contact (i.e., fellatio) (714–716). *N. meningitidis* has similar colony morphology appearance on culture and cannot be distinguished from *N. gonorrhoeae* on Gram stain. Identification of *N. meningitidis* as the etiologic agent with presumed gonococcal urethritis on the basis of Gram stain but negative NAAT for gonorrhea requires a confirmation by culture. Meningococcal urethritis is treated with the same antimicrobial regimens as gonococcal urethritis. Although evidence is limited regarding the risk for sexual transmission or recurrent infections with meningococcal urethritis, treatment of sex partners of patients with meningococcal urethritis with the same antimicrobial regimens as for exposure to gonococcal infection can be considered. No indication exists for treating

persons with *N. meningitidis* identified in their oropharynx when not also associated with symptomatic urethritis.

In other instances, NGU can be caused by HSV, Epstein-Barr virus, and adenovirus (699) acquired by fellatio (i.e., oral-penile contact). In a retrospective review of 80 cases of HSV urethritis in Australia (717), the majority of infections were associated with HSV-1 with clinical findings of meatitis (62%), genital ulceration (37%), and dysuria (20%). Adenovirus can present with dysuria, meatal inflammation, and conjunctivitis (718). Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse (699).

Other bacterial pathogens have been implicated as potential causes of clinical urethritis, either in clustered case series or as sporadic cases such as *Haemophilus influenzae* and *Haemophilus parainfluenzae* (719–723). *Haemophilus* was identified in 12.6% of cases among 413 men (mostly MSM reporting insertive oral sex) (724), and high rates of azithromycin resistance (39.5%) were identified among *Haemophilus* urethritis patients (725). Individual case reports have linked NGU to multiple bacterial species, including *Corynebacterium propinquum* (726), *Kurthia gibsonii* (727), *Corynebacterium glucuronolyticum* (728,729), *Corynebacterium striatum* (730), *Aerococcus urinae* (731), and *Neisseria elongata* (732). Diagnostic testing and treatment for less-common organisms are reserved for situations in which these infections are suspected (e.g., sexual partner with trichomoniasis, urethral lesions, or severe dysuria and meatitis) or when NGU is not responsive to recommended therapy.

Even in settings that provide comprehensive diagnostic testing, etiology can remain obscure in half of cases. Idiopathic NGU was reported in 772 (59%) of 1,295 first presentations of NGU among men seeking sexual health services in Australia (701). In a case-control study of 211 men with NGU symptoms in Denmark, no identifiable pathogen was identified in 24% of acute cases and 33% of chronic cases (733). NGU's importance if not caused by a defined pathogen is uncertain; neither complications (e.g., urethral stricture or epididymitis) nor adverse outcomes among sex partners have been identified in these cases.

Associations between NGU and insertive anal and oral exposure have been reported (734), as have higher rates of BV-associated *Leptotrichia* or *Sneathia* species among heterosexual men with urethritis (735). These studies increase concern for possible undetected infectious rectal or vaginal pathogens, or alternatively, a transient reactive dysbiosis after exposure to a new microbiome or even a noninfectious reactive etiology (736).

## Diagnostic Considerations

Clinicians should attempt to obtain objective evidence of urethral inflammation. If POC diagnostic tests (e.g., Gram stain or MB or GV microscopy) are unavailable, urethritis can be documented on the basis of any of the following signs or laboratory tests:

- Mucoid, mucopurulent, or purulent discharge on examination.
- Gram stain is a POC diagnostic test for evaluating urethritis that is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection; MB or GV stain of urethral secretions is an alternative POC diagnostic test with performance characteristics similar to Gram stain; thus, the cutoff number for WBCs per oil immersion field should be the same (737).
  - Presumed gonococcal infection is established by documenting the presence of WBCs containing GNID in Gram stain or intracellular purple diplococci in MB or GV smears; men should be tested for *C. trachomatis* and *N. gonorrhoeae* by NAATs and presumptively treated and managed accordingly for gonococcal infection (see Gonococcal Infections).
  - If no intracellular gram-negative or purple diplococci are present, men should receive NAATs for *C. trachomatis* and *N. gonorrhoeae* and can be managed for NGU as recommended (see Nongonococcal Urethritis).
  - Gram stain of urethral secretions exist that demonstrate  $\geq 2$  WBCs per oil immersion field (738). The microscopy diagnostic cutoff might vary, depending on background prevalence ( $\geq 2$  WBCs/high power field [HPF] in high-prevalence settings [STI clinics] or  $\geq 5$  WBCs/HPF in lower-prevalence settings). §§

§§ For urethral microscopy, the cutoff for diagnosing urethritis is  $\geq 2$  WBCs/HPF  
**Sources:** Rietmeijer CA, Mettenbrink CJ. Recalibrating the Gram stain diagnosis of male urethritis in the era of nucleic acid amplification testing. Sex Transm Dis 2012;39:18–20; Rietmeijer CA, Mettenbrink CJ. The diagnosis of nongonococcal urethritis in men: can there be a universal standard? Sex Transm Dis 2017;44:195–6. An additional evaluation supported this cutoff by demonstrating NGU sensitivity of 92.6% for cutoff of  $\geq 2$  versus 55.6% sensitivity for cutoff of  $\geq 5$  (**Source:** Sarier M, Sepin N, Duman I, et al. Microscopy of Gram-stained urethral smear in the diagnosis of urethritis: which threshold value should be selected? Andrologia 2018;50:e13143). Diagnostic cutoffs for 369 symptomatic and asymptomatic heterosexual men seeking STI care in Seattle revealed a maximal sensitivity and specificity achieved with a cutoff of  $\geq 5$  WBCs/HPF. Using a lower cutoff of  $\geq 2$  WBCs/HPF would miss 13% of *C. trachomatis* and *M. genitalium* and overtreat 45% of persons who have negative tests (**Source:** Leipertz G, Chambers L, Lowens S, et al. P796 Reassessing the Gram stain smear [GSS] polymorphonuclear leukocyte [PMN] cutoff for diagnosing non-gonococcal urethritis [NGU]. Sex Transm Infect 2019;95[Suppl 1]:A339). Another study discussed that the WBC/HPF cutoff value should discriminate on the basis of the prevalence of chlamydia, mycoplasma, and gonorrhea among a clinic population (**Source:** Moi H, Hartgill U, Skulderud KH, Reponen EJ, Syvertsen L, Moghaddam A. Microscopy of stained urethral smear in male urethritis: which cutoff should be used? Sex Transm Dis 2017;44:189–94).

- Positive leukocyte esterase test on first-void urine or microscopic examination of sediment from a spun first-void urine demonstrating  $\geq 10$  WBCs/HPE.

Men evaluated in settings in which Gram stain or MB or GV smear is unavailable who meet at least one criterion for urethritis (i.e., urethral discharge, positive leukocyte esterase test on first void urine, or microscopic examination of first-void urine sediment with  $\geq 10$  WBCs/HPE) should be tested for *C. trachomatis* and *N. gonorrhoeae* by NAATs and treated with regimens effective against gonorrhea and chlamydia.

If symptoms are present but no evidence of urethral inflammation is present, NAATs for *C. trachomatis* and *N. gonorrhoeae* might identify infections (739). Persons with chlamydia or gonorrhea should receive recommended treatment, and sex partners should be referred for evaluation and treatment. If none of these clinical criteria are present, empiric treatment of men with symptoms of urethritis is recommended only for those at high risk for infection who are unlikely to return for a follow-up evaluation or test results. Such men should be treated with drug regimens effective against gonorrhea and chlamydia.

## Nongonococcal Urethritis

NGU is a nonspecific diagnosis that can have various infectious etiologies. *C. trachomatis* has been well established as an NGU etiology; however, prevalence varies across populations and accounts for <50% of overall cases (712,740–742). *M. genitalium* is estimated to account for 10%–25% of cases (696,697,701,703,704,706,733,743), and *T. vaginalis* for 1%–8% of cases depending on population and location (703,706,708,710,712). Other etiologies include different bacteria, such as *Haemophilus* species (724,725), *N. meningitidis* (713,716), HSV (706,717), and adenovirus (744). However, even when extensive testing is performed, no pathogens are identified in approximately half of cases (701,733).

## Diagnostic Considerations

Clinical presentation can include urethral discharge, irritation, dysuria, or meatal pruritus (697,743,745). NGU is confirmed for symptomatic men when diagnostic evaluation of urethral secretions indicates inflammation, without evidence of diplococci by Gram, MB, or GV smear on microscopy (712,746,747). Visible discharge or secretions can be collected by a swab without inserting it into the urethra; if no visible secretions, the swab can be inserted into the urethral meatus and rotated, making contact with the urethral wall before removal. If microscopy is unavailable, urine testing for leukocyte esterase can be performed on first-void urine, and microscopic examination of sediment from a spun first-void

urine demonstrating  $\geq 10$  WBCs/HPE has a high negative predictive value.

All men who have suspected or confirmed NGU should be tested for chlamydia and gonorrhea by using NAATs. A specific diagnosis can potentially reduce complications, reinfection, and transmission. *M. genitalium* testing should be performed for men who have persistent or recurrent symptoms after initial empiric treatment. Testing for *T. vaginalis* should be considered in areas or among populations with high prevalence, in cases where a partner is known to be infected, or for men who have persistent or recurrent symptoms after initial empiric treatment.

## Treatment

Ideally, treatment should be pathogen based; however, diagnostic information might not be immediately available. Presumptive treatment should be initiated at NGU diagnosis. Doxycycline is highly effective for chlamydial urethral infections and is also effective for chlamydial infections of the rectum; it also has some activity against *M. genitalium*. In contrast, reports have increased of azithromycin treatment failures for chlamydial infection (748,749), and the incidence of macrolide resistance in *M. genitalium* also has been rapidly rising (697,702,705,750,751). Pharmacokinetic data indicate that changing azithromycin dosing from a single-dose strategy to a multiday strategy might protect against inducing resistance in *M. genitalium* infections (745,752) (see *Mycoplasma genitalium*).

### Recommended Regimen for Nongonococcal Urethritis

**Doxycycline** 100 mg orally 2 times/day for 7 days

### Alternative Regimens

**Azithromycin** 1 g orally in a single dose  
or

**Azithromycin** 500 mg orally in a single dose; then 250 mg orally daily for 4 days

To maximize compliance with recommended therapies, medications should be dispensed on-site at the clinic, and, regardless of the number of doses involved in the regimen, the first dose should be directly observed. Erythromycin is no longer recommended for NGU because of its gastrointestinal side effects and dosing frequency. Levofloxacin is no longer recommended for NGU because of its inferior efficacy, especially for *M. genitalium*.

## Management Considerations

To minimize transmission and reinfections, men treated for NGU should be instructed to abstain from sexual intercourse until they and their partners have been treated (i.e., until

completion of a 7-day regimen and symptoms have resolved or for 7 days after single-dose therapy). Men with NGU should be tested for HIV and syphilis.

## Follow-Up

Men should be provided their testing results obtained as part of the NGU evaluation. Those with a specific diagnosis of chlamydia, gonorrhea, or trichomoniasis should be offered partner services and instructed to return 3 months after treatment for repeat testing because of high rates of reinfection, regardless of whether their sex partners were treated (136,137,753,754) (see Chlamydial Infections; Gonococcal Infections; Trichomoniasis).

If symptoms persist or recur after therapy completion, men should be instructed to return for reevaluation and should be tested for *M. genitalium* and *T. vaginalis*. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are insufficient basis for retreatment. Providers should be alert to the possible diagnosis of chronic prostatitis or chronic pelvic pain syndrome in men experiencing persistent perineal, penile, or pelvic pain or discomfort; voiding symptoms; pain during or after ejaculation; or new-onset premature ejaculation lasting for >3 months. Men with persistent pain should be referred to a urologist with expertise in pelvic pain disorders.

## Management of Sex Partners

All sex partners of men with NGU within the preceding 60 days should be referred for evaluation and testing and presumptive treatment with a drug regimen effective against chlamydia. All partners should be evaluated and treated according to the management section for their respective pathogen; EPT could be an alternate approach if a partner is unable to access timely care. To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partners are treated.

## Persistent or Recurrent Nongonococcal Urethritis

The objective diagnosis of persistent or recurrent NGU should be made before considering additional antimicrobial therapy. Symptomatic recurrent or persistent urethritis might be caused by treatment failure or reinfection after successful treatment. Among men who have persistent symptoms after treatment without objective signs of urethral inflammation, the value of extending the duration of antimicrobials has not been demonstrated. Treatment failure for chlamydial urethritis has been estimated at 6%–12% (755). The most common cause of persistent or recurrent NGU is *M. genitalium*, especially after doxycycline therapy (756,757). Treatment failure for *M. genitalium* is harder to determine because certain men

achieve clinical cure (i.e., resolution of symptoms) but can still have detectable *M. genitalium* in urethral specimens (758).

The initial step in recurrent urethritis is assessing compliance with treatment or potential reexposure to an untreated sex partner (697,743). If the patient did not comply with the treatment regimen or was reexposed to an untreated partner, retreatment with the initial regimen can be considered. If therapy was appropriately completed and no reexposure occurred, therapy is dependent on the initial treatment regimen. Ideally, diagnostic testing among men with recurrent or persistent symptoms, including those with gonorrhea, chlamydia, *M. genitalium*, and trichomoniasis, can be used to guide further management decisions.

*T. vaginalis* is also known to cause urethritis among men who have sex with women. In areas where *T. vaginalis* is prevalent, men who have sex with women with persistent or recurrent urethritis should be tested for *T. vaginalis* and presumptively treated with metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose; their partners should be referred for evaluation and treatment, if needed.

If *T. vaginalis* is unlikely (MSM with NGU or negative *T. vaginalis* NAAT), men with recurrent NGU should be tested for *M. genitalium* by using an FDA-cleared NAAT. Treatment for *M. genitalium* includes a two-stage approach, ideally using resistance-guided therapy. If *M. genitalium* resistance testing is available it should be performed, and the results should be used to guide therapy (see *Mycoplasma genitalium*). If *M. genitalium* resistance testing is not available, doxycycline 100 mg orally 2 times/day for 7 days followed by moxifloxacin 400 mg orally once daily for 7 days should be used. The rationale for this approach is that although not curative, doxycycline decreases the *M. genitalium* bacterial load, thereby increasing likelihood of moxifloxacin success (759). Higher doses of azithromycin have not been effective for *M. genitalium* after azithromycin treatment failures. Men with persistent or recurrent NGU after treatment for *M. genitalium* or *T. vaginalis* should be referred to an infectious disease or urology specialist.

## Special Considerations

### HIV Infection

NGU might facilitate HIV transmission (760). Persons with NGU and HIV infection should receive the same treatment regimen as those who do not have HIV.

## Cervicitis

Two major diagnostic signs characterize cervicitis: 1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as mucopurulent cervicitis), and

2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Either or both signs might be present. Cervicitis frequently is asymptomatic; however, certain women might report an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g., especially after sexual intercourse). The criterion of using an increased number of WBCs on endocervical Gram stain in the diagnosis of cervicitis has not been standardized; it is not sensitive, has a low positive predictive value for *C. trachomatis* and *N. gonorrhoeae* infections, and is not available in most clinical settings (297,761). Leukorrhea, defined as >10 WBCs/HPF on microscopic examination of vaginal fluid, might be a sensitive indicator of cervical inflammation with a high negative predictive value (i.e., cervicitis is unlikely in the absence of leukorrhea) (762,763). Finally, although the presence of gram-negative intracellular diplococci on Gram stain of endocervical exudate might be specific for diagnosing gonococcal cervical infection when evaluated by an experienced laboratorian, it is not a sensitive indicator of infection (764).

## Etiology

*C. trachomatis* or *N. gonorrhoeae* is the most common etiology of cervicitis defined by diagnostic testing. Trichomoniasis, genital herpes (especially primary HSV-2 infection), or *M. genitalium* (761,765–768) also have been associated with cervicitis. However, in many cases of cervicitis, no organism is isolated, especially among women at relatively low risk for recent acquisition of these STIs (e.g., women aged >30 years) (769). Limited data indicate that BV and frequent douching might cause cervicitis (770–772). The majority of persistent cases of cervicitis are not caused by reinfection with *C. trachomatis* or *N. gonorrhoeae*; other factors might be involved (e.g., persistent abnormality of vaginal flora, *M. genitalium*, douching or exposure to other types of chemical irritants, dysplasia, or idiopathic inflammation in the zone of ectopy). Available data do not indicate an association between group B streptococcus colonization and cervicitis (773,774). No specific evidence exists for a role for *Ureaplasma parvum* or *Ureaplasma urealyticum* in cervicitis (707,761,765,775,776).

## Diagnostic Considerations

Because cervicitis might be a sign of upper genital tract infection (e.g., endometritis), women should be assessed for signs of PID and tested for *C. trachomatis* and *N. gonorrhoeae* with NAAT on vaginal, cervical, or urine samples (553) (see Chlamydial Infections; Gonococcal Infections). Women with cervicitis also should be evaluated for concomitant BV and trichomoniasis. Because sensitivity of microscopy for detecting *T. vaginalis* is relatively low (approximately 50%), symptomatic women with cervicitis and negative wet-mount

microscopy for trichomonads should receive further testing (i.e., NAAT, culture, or other FDA-cleared diagnostic test) (see Trichomoniasis). Testing for *M. genitalium* with the FDA-cleared NAAT can be considered. Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., PCR or culture) for HSV-2 is unknown. Testing for *U. parvum*, *U. urealyticum*, *Mycoplasma hominis*, or genital culture for group B streptococcus is not recommended.

## Treatment

Multiple factors should affect the decision to provide presumptive therapy for cervicitis. Presumptive treatment with antimicrobials for *C. trachomatis* and *N. gonorrhoeae* should be provided for women at increased risk (e.g., those aged <25 years and women with a new sex partner, a sex partner with concurrent partners, or a sex partner who has an STI), if follow-up cannot be ensured, or if testing with NAAT is not possible. Trichomoniasis and BV should be treated if detected (see Bacterial Vaginosis; Trichomoniasis). For women at lower risk for STIs, deferring treatment until results of diagnostic tests are available is an option. If treatment is deferred and *C. trachomatis* and *N. gonorrhoeae* NAATs are negative, a follow-up visit to determine whether the cervicitis has resolved can be considered.

### Recommended Regimen for Cervicitis\*

Doxycycline 100 mg orally 2 times/day for 7 days

\* Consider concurrent treatment for gonococcal infection if the patient is at risk for gonorrhea or lives in a community where the prevalence of gonorrhea is high (see Gonococcal Infections).

### Alternative Regimen

Azithromycin 1 g orally in a single dose

## Other Management Considerations

To minimize transmission and reinfection, women treated for cervicitis should be instructed to abstain from sexual intercourse until they and their partners have been treated (i.e., until completion of a 7-day regimen or for 7 days after single-dose therapy) and symptoms have resolved. Women who receive a cervicitis diagnosis should be tested for syphilis and HIV in addition to other recommended diagnostic tests.

## Follow-Up

Women receiving treatment should return to their provider for a follow-up visit to determine whether cervicitis has resolved. For women who are untreated, a follow-up visit gives providers an opportunity to communicate test results obtained as part of the cervicitis evaluation. Providers should treat on the basis of any positive test results and determine whether

cervicitis has resolved. Women with a specific diagnosis of chlamydia, gonorrhea, or trichomoniasis should be offered partner services and instructed to return in 3 months after treatment for repeat testing because of high rates of reinfection, regardless of whether their sex partners were treated (753). If symptoms persist or recur, women should be instructed to return for reevaluation.

### Management of Sex Partners

Management of sex partners of women treated for cervicitis should be tailored for the specific infection identified or suspected. All sex partners during the previous 60 days should be referred for evaluation, testing, and presumptive treatment if chlamydia, gonorrhea, or trichomoniasis was identified. EPT and other effective partner referral strategies are alternative approaches for treating male partners of women who have chlamydial or gonococcal infection (125–127) (see Partner Services). To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partners are treated.

### Persistent or Recurrent Cervicitis

Women with persistent or recurrent cervicitis despite antimicrobial therapy should be reevaluated for possible reexposure or treatment failure. If relapse or reinfection with a specific infection has been excluded, BV is not present, and sex partners have been evaluated and treated, management options for persistent cervicitis are undefined. In addition, the usefulness of repeated or prolonged administration of antimicrobial therapy for persistent symptomatic cervicitis remains unknown. The etiology of persistent cervicitis, including the potential role of *M. genitalium* (777), is unclear. *M. genitalium* might be considered for cases of cervicitis that persist after azithromycin or doxycycline therapy in which reexposure to an infected partner or medical nonadherence is unlikely. Among women with persistent cervicitis who were previously treated with doxycycline or azithromycin, testing for *M. genitalium* can be considered and treatment initiated on the basis of results of diagnostic testing (318) (see *Mycoplasma genitalium*). For women with persistent symptoms that are clearly attributable to cervicitis, referral to a gynecologic specialist can be considered for evaluation of noninfectious causes (e.g., cervical dysplasia or polyps) (778).

### Special Considerations

#### HIV Infection

Women with cervicitis and HIV infection should receive the same treatment regimen as those who do not have HIV. Cervicitis can increase cervical HIV shedding, and treatment reduces HIV shedding from the cervix and thereby might reduce HIV transmission to susceptible sex partners (779–783).

### Pregnancy

Diagnosis and treatment of cervicitis for pregnant women does not differ from that for women who are not pregnant (see Diagnostic Considerations; Treatment).

### Contraceptive Management

According to *U.S. Medical Eligibility Criteria for Contraceptive Use, 2016*, leaving an IUD in place during treatment for cervicitis is advisable (58). However, current recommendations specify that an IUD should not be placed if active cervicitis is diagnosed (59).

## Chlamydial Infections

### Chlamydial Infection Among Adolescents and Adults

Chlamydial infection is the most frequently reported bacterial infectious disease in the United States, and prevalence is highest among persons aged ≤24 years (141,784). Multiple sequelae can result from *C. trachomatis* infection among women, the most serious of which include PID, ectopic pregnancy, and infertility. Certain women who receive a diagnosis of uncomplicated cervical infection already have subclinical upper genital tract infection.

Asymptomatic infection is common among both men and women. To detect chlamydial infection, health care providers frequently rely on screening tests. Annual screening of all sexually active women aged <25 years is recommended, as is screening of older women at increased risk for infection (e.g., women aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) (149). In a community-based cohort of female college students, incident chlamydial infection was also associated with BV and high-risk HPV infection (785). Although chlamydia incidence might be higher among certain women aged ≥25 years in certain communities, overall, the largest proportion of infection is among women aged <25 years (141).

Chlamydia screening programs have been demonstrated to reduce PID rates among women (786,787). Although evidence is insufficient to recommend routine screening for *C. trachomatis* among sexually active young men because of certain factors (i.e., feasibility, efficacy, and cost-effectiveness), screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, or STD specialty clinics) or for populations with a high burden of infection (e.g., MSM) (149,788). Among women, the primary focus of

chlamydia screening should be to detect and treat chlamydia, prevent complications, and test and treat their partners, whereas targeted chlamydia screening for men should be considered only when resources permit, prevalence is high, and such screening does not hinder chlamydia screening efforts for women (789–791). More frequent screening than annual for certain women (e.g., adolescents) or certain men (e.g., MSM) might be indicated on the basis of risk behaviors.

## Diagnostic Considerations

For women, *C. trachomatis* urogenital infection can be diagnosed by vaginal or cervical swabs or first-void urine. For men, *C. trachomatis* urethral infection can be diagnosed by testing first-void urine or a urethral swab. NAATs are the most sensitive tests for these specimens and are the recommended test for detecting *C. trachomatis* infection (553). NAATs that are FDA cleared for use with vaginal swab specimens can be collected by a clinician or patient in a clinical setting. Patient-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs (792,793), and this screening strategy is highly acceptable among women (794,795). Optimal urogenital specimen types for chlamydia screening by using NAAT include first-catch urine (for men) and vaginal swabs (for women) (553). Recent studies have demonstrated that among men, NAAT performance on self-collected meatal swabs is comparable to patient-collected urine or provider-collected urethral swabs (796–798). Patient collection of a meatal swab for *C. trachomatis* testing might be a reasonable approach for men who are either unable to provide urine or prefer to collect their own meatal swab over providing urine. Previous evidence indicates that the liquid-based cytology specimens collected for Pap smears might be acceptable specimens for NAAT, although test sensitivity using these specimens might be lower than that associated with use of cervical or vaginal swab specimens (799); regardless, certain NAATs have been cleared by FDA for use on liquid-based cytology specimens.

Rectal and oropharyngeal *C. trachomatis* infection among persons engaging in receptive anal or oral intercourse can be diagnosed by testing at the anatomic exposure site. NAATs have been demonstrated to have improved sensitivity and specificity, compared with culture, for detecting *C. trachomatis* at rectal and oropharyngeal sites (553,800–804), and certain NAAT platforms have been cleared by FDA for these anatomic sites (805). Data indicate that NAAT performance on self-collected rectal swabs is comparable to clinician-collected rectal swabs, and this specimen collection strategy for rectal *C. trachomatis* screening is highly acceptable among men (217,806). Self-collected rectal swabs are a reasonable alternative to clinician-collected rectal swabs for *C. trachomatis*

screening by NAAT, especially when clinicians are not available or when self-collection is preferred over clinician collection. Annual screening for rectal *C. trachomatis* infection should be performed among men who report sexual activity at the rectal site. Exogenital chlamydial testing at the rectal site can be considered for females on the basis of reported sexual behaviors and exposure through shared clinical decision-making by the patient and the provider. The majority of persons with *C. trachomatis* detected at oropharyngeal sites do not have oropharyngeal symptoms. The clinical significance of oropharyngeal *C. trachomatis* infection is unclear, and prevalence is low, even among populations at high risk. However, when gonorrhea testing is performed at the oropharyngeal site, chlamydia test results might be reported because certain NAATs detect both bacteria from a single specimen.

POC tests for *C. trachomatis* among asymptomatic persons can expedite treatment of infected persons and their sex partners. Among symptomatic patients, POC tests for *C. trachomatis* can optimize treatment by limiting unnecessary presumptive treatment at the time of clinical decision-making and improve antimicrobial stewardship. Thus, using a POC test will likely be a cost-effective diagnostic strategy for *C. trachomatis* infection (807). Newer NAAT-based POC tests have promising performance and are becoming commercially available (807–809).

## Treatment

Treating persons with *C. trachomatis* prevents adverse reproductive health complications and continued sexual transmission. Furthermore, treating their sex partners can prevent reinfection and infection of other partners. Treating pregnant women usually prevents transmission of *C. trachomatis* to neonates during birth. Treatment should be provided promptly for all persons with chlamydial infection; treatment delays have been associated with complications (e.g., PID) in a limited proportion of women (810).

### Recommended Regimen for Chlamydial Infection Among Adolescents and Adults

Doxycycline 100 mg orally 2 times/day for 7 days

### Alternative Regimens

Azithromycin 1 g orally in a single dose

or

Levofloxacin 500 mg orally once daily for 7 days

A meta-analysis and a Cochrane systematic review evaluated data from randomized clinical trials of azithromycin versus doxycycline for treating urogenital chlamydial infection determined that microbiologic treatment failure among men was higher for azithromycin than for doxycycline (748,749).

Observational studies have also demonstrated that doxycycline is more efficacious for rectal *C. trachomatis* infection for men and women than azithromycin (748,811). A randomized trial for the treatment of rectal chlamydia infection among MSM reported microbiologic cure was 100% with doxycycline and 74% with azithromycin (812). A published review reported that *C. trachomatis* was detected at the anorectal site among 33%–83% of women who had urogenital *C. trachomatis* infection, and its detection was not associated with report of receptive anorectal sexual activity (813).

Although the clinical significance of oropharyngeal *C. trachomatis* infection is unclear and routine oropharyngeal screening is not recommended, oropharyngeal *C. trachomatis* can be sexually transmitted to genital sites (211,814); therefore, if *C. trachomatis* is identified from an oropharyngeal specimen while screening for pharyngeal gonorrhea, it should be treated. Evidence is limited regarding the efficacy of antimicrobial regimens for oropharyngeal chlamydia; however, a recently published observational study indicates doxycycline might be more efficacious than azithromycin for oropharyngeal chlamydia (815).

Available evidence supports that doxycycline is efficacious for *C. trachomatis* infections of urogenital, rectal, and oropharyngeal sites. Although azithromycin maintains high efficacy for urogenital *C. trachomatis* infection among women, concern exists regarding effectiveness of azithromycin for concomitant rectal *C. trachomatis* infection, which can occur commonly among women and cannot be predicted by reported sexual activity. Inadequately treated rectal *C. trachomatis* infection among women who have urogenital chlamydia can increase the risk for transmission and place women at risk for repeat urogenital *C. trachomatis* infection through autoinoculation from the anorectal site (816). Doxycycline is also available in a delayed-release 200-mg tablet formulation, which requires once-daily dosing for 7 days and is as effective as doxycycline 100 mg twice daily for 7 days for treating urogenital *C. trachomatis* infection in men and women. It is more costly but also has lower frequency of gastrointestinal side effects (817). Levofloxacin is an effective treatment alternative but is more expensive. Erythromycin is no longer recommended because of the frequency of gastrointestinal side effects, which can result in nonadherence. When nonadherence to doxycycline regimen is a substantial concern, azithromycin 1 g regimen is an alternative treatment option but might require posttreatment evaluation and testing because it has demonstrated lower treatment efficacy among persons with rectal infection.

Among persons receiving multidose regimens, medication should be dispensed with all doses involved, on-site and in the clinic, and the first dose should be directly observed. To

maximize adherence with recommended therapies, on-site, directly observed single-dose therapy with azithromycin should always be available for persons for whom adherence with multiday dosing is a considerable concern.

## Other Management Considerations

To minimize disease transmission to sex partners, persons treated for chlamydia should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen and resolution of symptoms if present. To minimize risk for reinfection, patients also should be instructed to abstain from sexual intercourse until all of their sex partners have been treated. Persons who receive a diagnosis of chlamydia should be tested for HIV, gonorrhea, and syphilis. MSM who are HIV negative with a rectal chlamydia diagnosis should be offered HIV PrEP.

## Follow-Up

Test of cure to detect therapeutic failure (i.e., repeat testing 4 weeks after completing therapy) is not advised for nonpregnant persons treated with the recommended or alternative regimens, unless therapeutic adherence is in question, symptoms persist, or reinfection is suspected. Moreover, using chlamydial NAATs at <4 weeks after completion of therapy is not recommended because the continued presence of nonviable organisms (553,818,819) can lead to false-positive results.

A high prevalence of *C. trachomatis* infection has been observed among women and men who were treated for chlamydial infection during the preceding months (753,755,820–822). The majority of posttreatment infections do not result from treatment failure but rather from reinfection caused by failure of sex partners to receive treatment or initiation of sexual activity with a new infected partner (823), indicating a need for improved education and treatment of sex partners. Repeat infections confer an elevated risk for PID and other complications among women. Men and women who have been treated for chlamydia should be retested approximately 3 months after treatment, regardless of whether they believe their sex partners were treated; scheduling the follow-up visit at the time of treatment is encouraged (753). If retesting at 3 months is not possible, clinicians should retest whenever persons next seek medical care <12 months after initial treatment.

## Management of Sex Partners

Sex partners should be referred for evaluation, testing, and presumptive treatment if they had sexual contact with the partner during the 60 days preceding the patient's onset of symptoms or chlamydia diagnosis. Although the exposure intervals defining identification of sex partners at risk are

based on limited data, the most recent sex partner should be evaluated and treated, even if the time of the last sexual contact was >60 days before symptom onset or diagnosis.

If health department partner management strategies (e.g., disease intervention specialists) are impractical or unavailable for persons with chlamydia, and if a provider is concerned that sex partners are unable to promptly access evaluation and treatment services, EPT should be considered as permitted by law (see Partner Services). Compared with standard patient referral of partners, this approach to therapy, which involves delivering the medication itself or a prescription by the patient or collaborating pharmacy, has been associated with decreased rates of persistent or recurrent chlamydia among women (125–127). Providers should provide patients with written educational materials to give to their partners about chlamydia, which should include notification that partners have been exposed and information about the importance of treatment. These materials also should inform partners about potential therapy-related allergies and adverse effects, along with symptoms indicative of complications (e.g., testicular pain among men and pelvic or abdominal pain among women). Educational materials for female partners should include information about the importance of seeking medical evaluation, especially if PID symptoms are present; undertreatment of PID among female partners and missed opportunities for diagnosing other STIs among women are concerning. MSM with chlamydia have a high risk for coexisting infections, especially undiagnosed HIV, among their partners and might have partners without HIV who could benefit from HIV PrEP. Data are also limited regarding effectiveness of EPT in reducing persistent or recurrent chlamydia among MSM (123,133,134); thus, shared clinical decision-making regarding EPT for MSM is recommended. Having partners accompany patients when they return for treatment is another strategy that has been used successfully for ensuring partner treatment (see Partner Services). To avoid reinfection, sex partners should be instructed to abstain from condomless sexual intercourse until they and their sex partners have been treated (i.e., after completion of a 7-day regimen) and any symptoms have resolved.

## Special Considerations

### Pregnancy

Clinical experience and published studies indicate that azithromycin is safe and effective during pregnancy (824–826). Doxycycline is contraindicated during the second and third trimesters of pregnancy because of risk for tooth discoloration. Human data reveal that levofloxacin presents a low risk to the fetus during pregnancy but has potential for toxicity during

breastfeeding; however, data from animal studies increase concerns regarding cartilage damage to neonates (431).

Test of cure (i.e., repeat testing after completion of therapy) to document chlamydial eradication, preferably by NAAT, at approximately 4 weeks after therapy completion during pregnancy is recommended because severe sequelae can occur among mothers and neonates if the infection persists. In addition, all pregnant women who have chlamydial infection diagnosed should be retested 3 months after treatment. Detection of *C. trachomatis* infection during the third semester is not uncommon among adolescent and young adult women, including those without *C. trachomatis* detected at the time of initial prenatal screening (827). Women aged <25 years and those at increased risk for chlamydia (i.e., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) should be screened at the first prenatal visit and rescreened during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant (149).

### Recommended Regimen for Chlamydial Infection During Pregnancy

Azithromycin 1 g orally in a single dose

### Alternative Regimen

Amoxicillin 500 mg orally 3 times/day for 7 days

Because of concerns regarding chlamydia persistence after exposure to penicillin-class antibiotics that has been demonstrated in animal and in vitro studies, amoxicillin is listed as an alternative therapy for *C. trachomatis* for pregnant women (828,829). Erythromycin is no longer recommended because of the frequency of gastrointestinal side effects that can result in therapy nonadherence. In addition, systematic reviews and meta-analyses have noted an association with macrolide antimicrobials, especially erythromycin, during pregnancy and adverse child outcomes, indicating cautious use in pregnancy (830–831).

### HIV Infection

Persons who have chlamydia and HIV infection should receive the same treatment regimen as those who do not have HIV.

## Chlamydial Infection Among Neonates

Prenatal screening and treatment of pregnant women is the best method for preventing chlamydial infection among neonates. *C. trachomatis* infection of neonates results from perinatal exposure to the mother's infected cervix. Initial *C. trachomatis* neonatal infection involves the mucous

membranes of the eye, oropharynx, urogenital tract, and rectum, although infection might be asymptomatic in these locations. Instead, *C. trachomatis* infection among neonates is most frequently recognized by conjunctivitis that develops 5–12 days after birth. *C. trachomatis* also can cause a subacute, afebrile pneumonia with onset at ages 1–3 months. Although *C. trachomatis* has been the most frequent identifiable infectious cause of ophthalmia neonatorum, neonatal chlamydial infections, including ophthalmia and pneumonia, have occurred less frequently since institution of widespread prenatal screening and treatment of pregnant women. Neonates born to mothers at high risk for chlamydial infection, with untreated chlamydia, or with no or unconfirmed prenatal care, are at high risk for infection. However, presumptive treatment of the neonate is not indicated because the efficacy of such treatment is unknown. Infants should be monitored to ensure prompt and age-appropriate treatment if symptoms develop. Processes should be in place to ensure communication between physicians and others caring for the mother and the newborn to ensure thorough monitoring of the newborn after birth.

### Ophthalmia Neonatorum Caused by *C. trachomatis*

A chlamydial etiology should be considered for all infants aged ≤30 days who experience conjunctivitis, especially if the mother has a history of chlamydial infection. These infants should receive evaluation and age-appropriate care and treatment.

### Preventing Ophthalmia Neonatorum Caused by *C. trachomatis*

Neonatal ocular prophylaxis with erythromycin, the only agent available in the United States for this purpose, is ineffective against chlamydial ophthalmia neonatorum (or pneumonia) (833). As an alternative, prevention efforts should focus on prenatal screening for *C. trachomatis*, including

- screening pregnant women at risk for *C. trachomatis* infection at the first prenatal visit (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI);
- treating all pregnant women with *C. trachomatis* during pregnancy and performing a test of cure 4 weeks after treatment to verify chlamydial eradication; these women should also be retested 3 months after treatment and again in the third trimester or at time of delivery, and their partners should also be tested and treated;
- retesting pregnant women during the third trimester who initially tested negative but remained at increased risk for acquiring infection (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one

sex partner, a sex partner with concurrent partners, or a sex partner who has an STI); and

- screening at delivery those pregnant women who were not screened for *C. trachomatis* during pregnancy if at risk or who had no prenatal care; physicians and others caring for the mother and the newborn should communicate to ensure follow-up on the results of laboratory tests performed at delivery, and if positive, prompt and age-appropriate treatment for the newborn and the mother.

Neonates born to mothers for whom prenatal chlamydia screening has been confirmed and the results are negative are not at high risk for infection.

### Diagnostic Considerations

Sensitive and specific methods for diagnosing chlamydial ophthalmia in the neonate include both tissue culture and nonculture tests (e.g., DFA tests and NAATs). DFA is the only nonculture FDA-cleared test for detecting chlamydia from conjunctival swabs. NAATs are not cleared by FDA for detecting chlamydia from conjunctival swabs, and clinical laboratories should verify the procedure according to CLIA regulations. Specimens for culture isolation and nonculture tests should be obtained from the everted eyelid by using a Dacron (DuPont)-tipped swab or the swab specified by the manufacturer's test kit; for culture and DFA, specimens must contain conjunctival cells, not exudate alone. Ocular specimens from neonates being evaluated for chlamydial conjunctivitis also should be tested for *N. gonorrhoeae* (see Ophthalmia Neonatorum Caused by *N. gonorrhoeae*).

### Treatment

#### Recommended Regimen for Chlamydial Infection Among Neonates

Erythromycin base or ethyl succinate 50 mg/kg body weight/day orally, divided into 4 doses daily for 14 days\*

\* An association between oral erythromycin and azithromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported among infants aged <6 weeks. Infants treated with either of these antimicrobials should be followed for IHPS signs and symptoms.

Although data regarding use of azithromycin for treating neonatal chlamydial infection are limited, available data demonstrate that a short therapy course might be effective (834). Topical antibiotic therapy alone is inadequate for treating ophthalmia neonatorum caused by chlamydia and is unnecessary when systemic treatment is administered.

### Follow-Up

Because the efficacy of erythromycin treatment for ophthalmia neonatorum is approximately 80%, a second course of therapy might be required (834,835). Data regarding

the efficacy of azithromycin for ophthalmia neonatorum are limited. Therefore, follow-up of infants is recommended to determine whether the initial treatment was effective. The possibility of concomitant chlamydial pneumonia should be considered (see Infant Pneumonia Caused by *C. trachomatis*).

### Management of Mothers and Their Sex Partners

Mothers of infants who have ophthalmia caused by chlamydia and the sex partners of these women should be evaluated and presumptively treated for chlamydia (see Chlamydial Infection Among Adolescents and Adults).

### Infant Pneumonia Caused by *C. trachomatis*

Chlamydial pneumonia among infants typically occurs at age 1–3 months and is a subacute pneumonia. Characteristic signs of chlamydial pneumonia among infants include a repetitive staccato cough with tachypnea and hyperinflation and bilateral diffuse infiltrates on a chest radiograph. In addition, peripheral eosinophilia ( $\geq 400$  cells/mm $^3$ ) occurs frequently. Because clinical presentations differ, all infants aged 1–3 months suspected of having pneumonia, especially those whose mothers have a history of, are at risk for (e.g., aged <25 years and those aged  $\geq 25$  years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI), or suspected of having a chlamydial infection should be tested for *C. trachomatis* and treated if infected.

### Diagnostic Considerations

Specimens for chlamydial testing should be collected from the nasopharynx. Tissue culture is the definitive standard diagnostic test for chlamydial pneumonia. Nonculture tests (e.g., DFA and NAAT) can be used. DFA is the only nonculture FDA-cleared test for detecting *C. trachomatis* from nasopharyngeal specimens; however, DFA of nasopharyngeal specimens has a lower sensitivity and specificity than culture. NAATs are not cleared by FDA for detecting chlamydia from nasopharyngeal specimens, and clinical laboratories should verify the procedure according to CLIA regulations (553). Tracheal aspirates and lung biopsy specimens, if collected, should be tested for *C. trachomatis*.

### Treatment

Because test results for chlamydia often are unavailable at the time initial treatment decisions are being made, treatment for *C. trachomatis* pneumonia frequently is based on clinical and radiologic findings, age of the infant (i.e., 1–3 months), and risk for chlamydia in the mother (i.e., aged <25 years, history of chlamydial infection, multiple sex partners, a sex partner with a concurrent partner, or a sex partner with a history of

an STI). In the absence of laboratory results in a situation with a high degree of suspicion of chlamydial infection and the mother is unlikely to return with the infant for follow-up, exposed infants can be presumptively treated with the shorter-course regimen of azithromycin 20 mg/kg body weight/day orally, 1 dose daily for 3 days.

#### Recommended Regimen for Chlamydial Pneumonia Among Infants

Erythromycin base or ethyl succinate 50 mg/kg body weight/day orally divided into 4 doses daily for 14 days

#### Alternative Regimen

Azithromycin suspension 20 mg/kg body weight/day orally, 1 dose daily for 3 days

### Follow-Up

Because erythromycin effectiveness in treating pneumonia caused by *C. trachomatis* is approximately 80%, a second course of therapy might be required (836). Data regarding effectiveness of azithromycin in treating chlamydial pneumonia are limited. Follow-up of infants is recommended to determine whether the pneumonia has resolved, although certain infants with chlamydial pneumonia continue to have abnormal pulmonary function tests later during childhood.

### Management of Mothers and Their Sex Partners

Mothers of infants who have chlamydial pneumonia and the sex partners of these women should be evaluated, tested, and presumptively treated for chlamydia (see Chlamydial Infection Among Adolescents and Adults).

### Chlamydial Infection Among Infants and Children

Sexual abuse should be considered a cause of chlamydial infection among infants and children. However, perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract, and rectum can persist for 2–3 years (see Sexual Assault or Abuse of Children).

### Diagnostic Considerations

NAATs can be used to test vaginal and urine specimens from girls and urine in boys (see Sexual Assault or Abuse of Children). Data are lacking regarding use of NAATs for specimens from extragenital sites (rectum and pharynx) among boys and girls (553); other nonculture tests (e.g., DFA) are not recommended because of specificity concerns. Although data regarding NAATs for specimens from extragenital sites for children are more limited and performance is test dependent (553), no evidence supports that NAAT performance

for detecting *C. trachomatis* for extragenital sites among children would differ from that among adults. Because of the implications of a diagnosis of *C. trachomatis* infection in a child, only CLIA-validated, FDA-cleared NAAT should be used for extragenital site specimens (837).

#### Recommended Regimens for Chlamydial Infection Among Infants and Children

**For infants and children weighing <45 kg:** Erythromycin base or ethyl succinate 50 mg/kg body weight/day orally divided into 4 doses daily for 14 days

Data are limited regarding the effectiveness and optimal dose of azithromycin for treating chlamydial infection among infants and children weighing <45 kg.

**For children weighing ≥45 kg but aged <8 years:** Azithromycin 1 g orally in a single dose

**For children aged ≥8 years:** Azithromycin 1 g orally in a single dose  
or  
Doxycycline 100 mg orally 2 times/day for 7 days

inconsistent condom use among persons who are not in mutually monogamous relationships, previous or coexisting STIs, and exchanging sex for money or drugs. Clinicians should consider the communities they serve and consult local public health authorities for guidance regarding identifying groups at increased risk. Gonococcal infection, in particular, is concentrated in specific geographic locations and communities. MSM at high risk for gonococcal infection (e.g., those with multiple anonymous partners or substance abuse) or those at risk for HIV acquisition should be screened at all anatomic sites of exposure every 3–6 months (see Men Who Have Sex with Men). At least annual screening is recommended for all MSM. Screening for gonorrhea among heterosexual men and women aged >25 years who are at low risk for infection is not recommended (149). A recent travel history with sexual contacts outside the United States should be part of any gonorrhea evaluation.

#### Diagnostic Considerations

Specific microbiologic diagnosis of *N. gonorrhoeae* infection should be performed for all persons at risk for or suspected of having gonorrhea; a specific diagnosis can potentially reduce complications, reinfections, and transmission. Culture, NAAT, and POC NAAT, such as GeneXpert (Cepheid), are available for detecting genitourinary infection with *N. gonorrhoeae* (149); culture requires endocervical (women) or urethral (men) swab specimens. Culture is also available for detecting rectal, oropharyngeal, and conjunctival gonococcal infection. NAATs and POC NAATs allow for the widest variety of FDA-cleared specimen types, including endocervical and vaginal swabs and urine for women, urethral swabs and urine for men, and rectal swabs and pharyngeal swabs for men and women ([www.accessdata.fda.gov/cdrh\\_docs/reviews/K121710.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K121710.pdf)). However, product inserts for each NAAT manufacturer should be consulted carefully because collection methods and specimen types vary. Certain NAATs that have been demonstrated to detect commensal *Neisseria* species might have comparable low specificity when testing oropharyngeal specimens for *N. gonorrhoeae* (553). NAAT sensitivity for detecting *N. gonorrhoeae* from urogenital and nongenital anatomic sites is superior to culture but varies by NAAT type (553,800–803). For urogenital infections, optimal specimen types for gonorrhea screening using NAATs include first-void urine for men and vaginal swab specimens for women (553). Patient-collected samples can be used in place of provider-collected samples in clinical settings when testing by NAAT for urine (men and women), vaginal swabs, rectal swabs, and oropharyngeal swabs after patient instructions have been provided (209,806,839–842). Patient-collected specimens

#### Other Management Considerations

See Sexual Assault or Abuse of Children.

#### Follow-Up

A test of cure to detect therapeutic failure ensures treatment effectiveness and should be obtained at a follow-up visit approximately 4 weeks after treatment is completed.

## Gonococcal Infections

### Gonococcal Infection Among Adolescents and Adults

In the United States, an estimated 1,568,000 new *N. gonorrhoeae* infections occur each year (141,838), and gonorrhea is the second most commonly reported bacterial communicable disease. Urethral infections caused by *N. gonorrhoeae* can produce symptoms among men that cause them to seek curative treatment soon enough to prevent sequelae, but often not soon enough to prevent transmission to others. Among women, gonococcal infections are commonly asymptomatic or might not produce recognizable symptoms until complications (e.g., PID) have occurred. PID can result in tubal scarring that can lead to infertility or ectopic pregnancy.

Annual screening for *N. gonorrhoeae* infection is recommended for all sexually active women aged <25 years and for older women at increased risk for infection (e.g., those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) (149). Additional risk factors for gonorrhea include

are reasonable alternatives to provider-collected swabs for gonorrhea screening by NAAT.

In cases of suspected or documented treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing because NAATs cannot provide antimicrobial susceptibility results. Because *N. gonorrhoeae* has demanding nutritional and environmental growth requirements, optimal recovery rates are achieved when specimens are inoculated directly and when the growth medium is promptly incubated in an increased carbon dioxide ( $\text{CO}_2$ ) environment (553). Nonnutritive swab transport systems are available that might maintain gonococcal viability for <48 hours in ambient temperatures (843–845).

Because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of urethral discharge or secretions that demonstrate polymorphonuclear leukocytes with intracellular gram-negative diplococci can be considered diagnostic for infection with *N. gonorrhoeae* among symptomatic men. However, because of lower sensitivity, a negative Gram stain should not be considered sufficient for ruling out infection among asymptomatic men. Infection detection by using Gram stain of endocervical, pharyngeal, and rectal specimens also is insensitive and is not recommended. MB or GV stain of urethral secretions is an alternative POC diagnostic test with performance characteristics similar to Gram stain. Gonococcal infection is diagnosed among symptomatic men by documenting the presence of a WBC-containing intracellular purple diplococci in MB or GV smears.

### **Antimicrobial-Resistant *N. gonorrhoeae***

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobials (846–848). In 1986, the Gonococcal Isolate Surveillance Project (GISP), a national sentinel surveillance system, was established to monitor trends in antimicrobial susceptibilities of urethral *N. gonorrhoeae* strains in the United States (849). The epidemiology of antimicrobial resistance guides decisions about gonococcal treatment recommendations and has evolved because of shifts in antimicrobial resistance patterns. During 2007, emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States prompted CDC to cease recommending fluoroquinolones for gonorrhea treatment, leaving cephalosporins as the only remaining class of antimicrobials available for gonorrhea treatment in the United States (850). Reflecting concern about emerging gonococcal resistance, CDC's 2010 STD treatment guidelines recommended dual therapy for gonorrhea with a cephalosporin plus either azithromycin or doxycycline, even if NAAT for *C. trachomatis* was negative at the time of treatment (851). However, during 2006–2011, the minimum concentrations of

cefixime needed to inhibit in vitro growth of the *N. gonorrhoeae* strains circulating in the United States and other countries increased, demonstrating that cefixime effectiveness might be waning (851). In addition, treatment failures with cefixime or other oral cephalosporins were reported in Asia (852–855), Europe (856–860), South Africa (861), and Canada (862,863). During that time, case reports of ceftriaxone treatment failures for pharyngeal infections reported in Australia (864,865), Japan (866), and Europe were concerning (856,867). Consequently, CDC no longer recommends cefixime as a first-line regimen for gonorrhea treatment in the United States (868). Since 2013, the proportion of GISP isolates that demonstrate reduced susceptibility (minimal inhibitory concentration [MIC]  $\geq 2.0 \mu\text{g/mL}$ ) to azithromycin has increased almost tenfold, to 5.1% in 2019 (141). Unlike the appearance of ciprofloxacin resistance in the early 2000s, and cefixime reduced-susceptibility isolates during 2010–2011, emergence of azithromycin resistance is not concentrated among certain populations (e.g., MSM in the western United States). Azithromycin has unique pharmacokinetic properties that might predispose to resistance due to its prolonged half-life (869,870). With the exception of a small cluster of gonorrhea strains with azithromycin resistance and reduced susceptibility to cefixime and ceftriaxone among seven patients during 2016, all gonorrhea strains identified by GISP are susceptible to either or both azithromycin and ceftriaxone or cefixime. In addition, since 2013, antimicrobial stewardship has become an urgent public health concern in the United States as described in *Antimicrobial Resistant Threats in the United States* (871). Emergence of azithromycin resistance is not isolated to *N. gonorrhoeae*; it has also been demonstrated in *M. genitalium* and such enteric pathogens as *Shigella* and *Campylobacter* (see *Mycoplasma genitalium*; Proctitis, Proctocolitis, and Enteritis). Finally, concern exists regarding azithromycin treatment efficacy for chlamydia (see Chlamydial Infections).

Dual therapy for gonococcal infection with ceftriaxone and azithromycin recommended in previous guidance might have mitigated emergence of reduced susceptibility to ceftriaxone in *N. gonorrhoeae*; however, concerns regarding potential harm to the microbiome and the effect on other pathogens diminishes the benefits of maintaining dual therapy. Consequently, only ceftriaxone is recommended for treating gonorrhea in the United States (872). Clinicians remaining vigilant for treatment failures is paramount, and CDC plans to continue to monitor for changing ceftriaxone MICs until additional antimicrobials or a vaccine is available. In cases in which chlamydial infection has not been excluded, patients should also receive antichlamydial therapy. CDC and state health departments participate in CDC-supported gonorrhea surveillance activities

(<https://www.cdc.gov/std/gisp>) and can provide the most current information regarding gonococcal susceptibility.

Criteria for resistance to cefixime and ceftriaxone have not been defined by the Clinical and Laboratory Standards Institute (CLSI). However, isolates with cefixime or ceftriaxone MICs  $\geq 0.5 \mu\text{g/mL}$  are considered to have decreased susceptibility (873). In the United States, the proportion of isolates in GISP demonstrating decreased susceptibility to ceftriaxone or cefixime has remained low; during 2019, <0.1% of isolates with decreased susceptibility (MIC  $\geq 0.5 \mu\text{g/mL}$ ) to ceftriaxone or cefixime were identified (141). Because increasing MICs might predict resistance emergence, GISP established lower cephalosporin MIC threshold values that are lower than the susceptibility breakpoints set by CLSI to provide greater sensitivity in detecting decreasing gonococcal susceptibility for surveillance purposes. The percentage of isolates with cefixime MICs  $\geq 0.25 \mu\text{g/mL}$  increased from 0.1% during 2006 to 1.4% during 2011 (851,874) and declined to 0.3% during 2019 (141). The percentage of isolates with ceftriaxone MICs  $\geq 0.125 \mu\text{g/mL}$  increased from <0.1% in 2006 to 0.4% in 2011 and decreased to 0.1% in 2019 (141). Isolates with high-level cefixime and ceftriaxone MICs (MICs = 1.5–8.0  $\mu\text{g/mL}$  and MICs = 1.5–4.0  $\mu\text{g/mL}$ , respectively) have been identified in Japan (866), France (867,875), Spain (876,877), the United Kingdom, and Australia (878,879). Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue; state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations (846,847). Although approximately 3% of all U.S. men who have gonococcal infections are sampled through GISP, surveillance by clinicians also is crucial. Clinicians who diagnose *N. gonorrhoeae* infection in a person with suspected cephalosporin treatment failure should perform culture and AST of relevant clinical specimens, consult an infectious disease specialist or an STD clinical expert (<https://www.stdccn.org/render/Public>) for guidance in clinical management, and report the case to CDC through state and local public health authorities within 24 hours. Isolates should be saved and sent to CDC through local and state public health laboratory mechanisms. Health departments should prioritize notification and culture evaluation for sexual partners of persons with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or persons whose isolates demonstrate decreased susceptibility to cephalosporin. Agar dilution is the reference standard and preferred method of antimicrobial susceptibility testing with *N. gonorrhoeae*. Antibiotic gradient strips, such as Etest (bioMérieux), can be used and are considered an acceptable alternative for quantitative antimicrobial susceptibility testing with

*N. gonorrhoeae* when manufacturer instructions are followed. Disc diffusion only provides qualitative susceptibility results.

## Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum

### Recommended Regimen for Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum Among Adults and Adolescents

Ceftriaxone 500 mg\* IM in a single dose for persons weighing <150 kg

If chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

\* For persons weighing  $\geq 150$  kg, 1 g ceftriaxone should be administered.

Although clinical data confirm that a single injection of ceftriaxone 250 mg is >99% (95% confidence interval [CI]: 97.6%–99.7%) effective in curing anogenital gonorrhea of circulating isolates (MIC = 0.03  $\mu\text{g/mL}$ ), a higher dose is likely necessary for isolates with elevated MICs (880,881). Effective treatment of uncomplicated urogenital gonorrhea with ceftriaxone requires concentrations higher than the strain MIC for approximately 24 hours; although individual variability exists in the pharmacokinetics of ceftriaxone, a 500-mg dose of ceftriaxone is expected to achieve in approximately 50 hours MIC  $>0.03 \mu\text{g/mL}$  (880,881). The pharmacokinetics of ceftriaxone might be different in the pharynx with longer times higher than the strain MIC likely needed to prevent selection of mutant strains in the pharynx (882).

Single-dose injectable cephalosporin regimens, other than ceftriaxone, that are safe and have been effective against uncomplicated urogenital and anorectal gonococcal infections in the past include ceftizoxime (500 mg IM), cefoxitin (2 g IM with probenecid 1 g orally), and cefotaxime (500 mg IM). None of these injectable cephalosporins offer any advantage over ceftriaxone 250 mg for urogenital infection, and efficacy for pharyngeal infection is less certain (883,884). Because the ceftriaxone dose has been increased and the pharmacokinetics of other cephalosporins have not been evaluated, these dosing regimens might be at a disadvantage over ceftriaxone 500 mg.

### Alternative Regimens if Ceftriaxone Is Not Available

Gentamicin 240 mg IM in a single dose

plus

Azithromycin 2 g orally in a single dose

or

Cefixime\* 800 mg orally in a single dose

\* If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

In one clinical trial, dual treatment with single doses of IM gentamicin 240 mg plus oral azithromycin 2 g cured 100% of cases (lower one-sided 95% CI bound: 98.5%) and

can be considered an alternative to ceftriaxone for persons with cephalosporin allergy (885). This trial was not powered enough to provide reliable estimates of the efficacy of these regimens for treatment of rectal or pharyngeal infection; however, this regimen cured the few extragenital infections among study participants. Notably, gastrointestinal adverse events, primarily vomiting <1 hour after dosing, occurred among 3%–4% of persons treated with gentamicin plus azithromycin, necessitating retreatment with ceftriaxone and azithromycin. A similar trial that studied gentamicin 240 mg plus azithromycin 1 g determined lower cure rates at extragenital sites; 80% (95% CI: 72%–88%) of pharyngeal and 90% (95% CI: 84%–95%) of rectal infections were cured with this regimen (886). Gemifloxacin plus azithromycin has been studied and is no longer recommended as an alternative regimen because of limited availability, cost, and antimicrobial stewardship concerns (885).

An 800-mg oral dose of cefixime should be considered only as an alternative cephalosporin regimen because it does not provide as high, nor as sustained, bactericidal blood levels as a 500-mg IM dose of ceftriaxone. Furthermore, it demonstrates limited efficacy for treatment of pharyngeal gonorrhea (92.3% cure; 95% CI: 74.9%–99.1%); in older clinical studies, cefixime cured 97.5% of uncomplicated urogenital and anorectal gonococcal infections (95% CI: 95.4%–99.8%) (883,884). The increase in the prevalence of isolates obtained through GISP with elevated cefixime MICs might indicate early stages of development of clinically significant gonococcal resistance to cephalosporins. Changes in cefixime MICs can result in decreasing effectiveness of cefixime for treating urogenital gonorrhea. Furthermore, as cefixime becomes less effective, continued used of cefixime might hasten the development of resistance to ceftriaxone, a safe, well-tolerated, injectable cephalosporin and the last antimicrobial known to be highly effective in a single dose for treatment of gonorrhea at all anatomic infection sites. Other oral cephalosporins (e.g., cefpodoxime and cefuroxime) are not recommended because of inferior efficacy and less favorable pharmacodynamics (883).

Monotherapy with azithromycin 2 g orally as a single dose has been demonstrated to be 99.2% effective against uncomplicated urogenital gonorrhea (95% CI: 97.3%–99.9%) (883). However, monotherapy is not recommended because of concerns about the ease with which *N. gonorrhoeae* can develop resistance to macrolides, the high proportion of isolates with azithromycin decreased susceptibility, and documented azithromycin treatment failures (859). Strains of *N. gonorrhoeae* circulating in the United States are not adequately susceptible to penicillin, tetracycline, and older macrolides (e.g., erythromycin), and thus use of these antimicrobials cannot be recommended.

Spectinomycin is effective (98.2% in curing uncomplicated urogenital and anorectal gonococcal infections) but has poor efficacy for pharyngeal infections (883,887). It is unavailable in the United States, and the gentamicin alternative regimen has replaced the need for spectinomycin, if a cephalosporin allergy exists, in the United States.

## Uncomplicated Gonococcal Infection of the Pharynx

The majority of gonococcal infections of the pharynx are asymptomatic and can be relatively common among certain populations (800,801,888–890). Although these infections rarely cause complications, they have been reported to be a major source of community transmission and might be a driver of antimicrobial resistance (891,892). Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites (862). Few antimicrobial regimens reliably cure >90% of gonococcal pharyngeal infections (883,884). Providers should ask their patients with urogenital or rectal gonorrhea about oral sexual exposure; if reported, pharyngeal testing should be performed.

### Recommended Regimen for Uncomplicated Gonococcal Infection of the Pharynx Among Adolescents and Adults

Ceftriaxone 500 mg\* IM in a single dose for persons weighing <150 kg

\* For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.

If chlamydial infection is identified when pharyngeal gonorrhea testing is performed, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days. No reliable alternative treatments are available for pharyngeal gonorrhea. For persons with an anaphylactic or other severe reaction (e.g., Stevens Johnson syndrome) to ceftriaxone, consult an infectious disease specialist for an alternative treatment recommendation.

## Other Management Considerations

To maximize adherence with recommended therapies and reduce complications and transmission, medication for gonococcal infection should be provided on-site and directly observed. If medications are unavailable when treatment is indicated, linkage to an STI treatment facility should be provided for same-day treatment. To minimize disease transmission, persons treated for gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are treated (7 days after receiving treatment and resolution of symptoms, if present). All persons who receive a diagnosis of gonorrhea should be tested for other STIs, including chlamydia, syphilis, and HIV.

Those persons whose HIV test results are negative should be offered HIV PrEP.

## Follow-Up

A test of cure (i.e., repeat testing after completion of therapy) is unnecessary for persons who receive a diagnosis of uncomplicated urogenital or rectal gonorrhea who are treated with any of the recommended or alternative regimens. Any person with pharyngeal gonorrhea should return 7–14 days after initial treatment for a test of cure by using either culture or NAAT; however, testing at 7 days might result in an increased likelihood of false-positive tests. If the NAAT is positive, effort should be made to perform a confirmatory culture before retreatment, especially if a culture was not already collected. All positive cultures for test of cure should undergo antimicrobial susceptibility testing. Symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT) and antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by other organisms (see Urethritis; Cervicitis; Proctitis).

A high prevalence of *N. gonorrhoeae* infection has been observed among men and women previously treated for gonorrhea (137,753,754,893). The majority of these infections result from reinfection caused by failure of sex partners to receive treatment or the initiation of sexual activity with a new infected partner, indicating a need for improved patient education and treatment of sex partners. Men or women who have been treated for gonorrhea should be retested 3 months after treatment regardless of whether they believe their sex partners were treated; scheduling the follow-up visit at the time of treatment is encouraged. If retesting at 3 months is not possible, clinicians should retest whenever persons next seek medical care <12 months after initial treatment.

## Management of Sex Partners

Recent sex partners (i.e., persons having sexual contact with the infected patient <60 days preceding onset of symptoms or gonorrhea diagnosis) should be referred for evaluation, testing, and presumptive treatment. If the patient's last potential sexual exposure was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated.

If health department partner-management strategies (e.g., disease intervention specialists) are impractical or unavailable for persons with gonorrhea and partners' access to prompt clinical evaluation and treatment is limited, EPT can be delivered to the partner by the patient or a collaborating pharmacy as permitted by law (see Partner Services). Treatment of the sexual partner with cefixime 800 mg as a single dose is recommended, provided that concurrent chlamydial infection has been excluded. If a chlamydia test result has not

been documented, the partner may be treated with a single dose of oral cefixime 800 mg plus oral doxycycline 100 mg 2 times/day for 7 days. If adherence with multiday dosing is a considerable concern, azithromycin 1 g can be considered but has lower treatment efficacy among persons with rectal chlamydia (see Chlamydial Infections). Provision of medication by EPT should be accompanied by written materials (125,127) for educating partners about gonorrhea, their exposure to gonorrhea, and the importance of therapy. These materials should also educate partners about seeking clinical evaluation for adverse reactions or complications and general follow-up when able. Educational materials for female partners should include information about the importance of seeking medical evaluation for PID, especially if symptomatic; undertreatment of PID among female partners and missed opportunities for diagnosing other STIs among women are of concern. MSM with gonorrhea have a high risk for coexisting infections (especially undiagnosed HIV) among their partners, and they might have partners without HIV who could benefit from PrEP. Data are also limited regarding the effectiveness of EPT in reducing persistent or recurrent gonorrhea among MSM (133,135); thus, shared clinical decision-making regarding EPT for MSM is recommended (see Partner Services). To avoid reinfection, sex partners should be instructed to abstain from condomless sexual intercourse for 7 days after they and their sex partners have completed treatment and after resolution of symptoms, if present.

## Suspected Cephalosporin Treatment Failure

Cephalosporin treatment failure is the persistence of *N. gonorrhoeae* infection despite recommended cephalosporin treatment; such failure is indicative of infection with cephalosporin-resistant gonorrhea among persons whose partners were treated and whose risk for reinfection is low. Suspected treatment failure has been reported among persons receiving oral and injectable cephalosporins (852–855,857,859,861,863,864,867,875,894). Treatment failure should be considered for persons whose symptoms do not resolve within 3–5 days after recommended treatment and report no sexual contact during the posttreatment follow-up period and persons with a positive test of cure (i.e., positive culture >72 hours or positive NAAT >7 days after receiving recommended treatment) when no sexual contact is reported during the posttreatment follow-up period (874). Treatment failure should also be considered for persons who have a positive culture on test of cure, if obtained, if evidence exists of decreased susceptibility to cephalosporins on antimicrobial susceptibility testing, regardless of whether sexual contact is reported during the posttreatment follow-up period.

The majority of suspected treatment failures in the United States are likely to be reinfections rather than actual treatment failures (137,753,754,894). However, in cases in which reinfection is unlikely and treatment failure is suspected, before retreatment, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing if *N. gonorrhoeae* is isolated. Phenotypic antimicrobial susceptibility testing should be performed by using Etest or agar dilution. All isolates of suspected treatment failures should be sent to CDC for antimicrobial susceptibility testing by agar dilution; local laboratories should store isolates for possible further testing if needed. Testing or storage of specimens or isolates should be facilitated by the state or local health department according to local public health protocol. Instructions for shipping isolates to CDC are available at [https://www.cdc.gov/std/gonorrhea/arg/specimen\\_shipping\\_instructions1-29-08.pdf](https://www.cdc.gov/std/gonorrhea/arg/specimen_shipping_instructions1-29-08.pdf).

For persons with suspected cephalosporin treatment failure, the treating clinician should consult an infectious disease specialist, the National Network of STD Clinical Prevention Training Center clinical consultation line (<https://www.stdccn.org/render/Public>), the local or state health department STI program, or CDC (telephone: 800-232-4636) for advice about obtaining cultures, antimicrobial susceptibility testing and treatment. Suspected treatment failure should be reported to CDC through the local or state health department <24 hours after diagnosis.

Patients with suspected treatment failures should first be retreated routinely with the initial regimen used (ceftriaxone 500 mg IM), with the addition of doxycycline if chlamydia infection exists, because reinfections are more likely than actual treatment failures. However, in situations with a higher likelihood of treatment failure than reinfection, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing before retreatment. Dual treatment with single doses of IM gentamicin 240 mg plus oral azithromycin 2 g can be considered, particularly when isolates are identified as having elevated cephalosporin MICs (885,886,895). Persons with suspected treatment failure after treatment with the alternative regimen (cefixime or gentamicin) should be treated with ceftriaxone 500 mg as a single IM dose or as a single dose with or without an antichlamydial agent on the basis of chlamydia infection status. A test of cure at relevant clinical sites should be obtained 7–14 days after retreatment; culture is the recommended test, preferably with simultaneous NAAT, and antimicrobial susceptibility testing of *N. gonorrhoeae* if isolated. Clinicians should ensure that the patients' sex partners from the preceding 60 days are evaluated promptly with culture

and presumptively treated by using the same regimen used for the patients.

## Special Considerations

### Drug Allergy, Intolerance, and Adverse Reactions

The risk for penicillin cross-reactivity is highest with first-generation cephalosporins but is rare (<1%) with third-generation cephalosporins (e.g., ceftriaxone and cefixime) (631,680,896). Clinicians should first thoroughly assess a patient's allergy history, including type of reaction, associated medications, and previous prescription records. If IgE-mediated penicillin allergy is strongly suspected, dual treatment with single doses of IM gentamicin 240 mg plus oral azithromycin 2 g can be administered (885,886). If a patient is asymptomatic and the treating facility is able to perform gyrase A (*gyrA*) testing to identify ciprofloxacin susceptibility (wild type), oral ciprofloxacin 500 mg in a single dose can be administered. Providers treating persons with IgE-mediated cephalosporin or penicillin allergy should refer to the section of these guidelines regarding evaluation (see Management of Persons Who Have a History of Penicillin Allergy).

### Pregnancy

Pregnant women infected with *N. gonorrhoeae* should be treated with ceftriaxone 500 mg in a single IM dose plus treatment for chlamydia if infection has not been excluded. When cephalosporin allergy or other considerations preclude treatment with this regimen, consultation with an infectious disease specialist or an STD clinical expert is recommended. Gentamicin use is cautioned during pregnancy because of risk for neonatal birth defects, nephrotoxicity, or ototoxicity (897) (<https://www.stdccn.org/render/Public>).

### HIV Infection

Persons who have gonorrhea and HIV infection should receive the same treatment regimen as those who do not have HIV.

### Gonococcal Conjunctivitis

In the only published study of the treatment regarding gonococcal conjunctivitis among adults, all 12 study participants responded to a single 1-g IM injection of ceftriaxone (898). Because gonococcal conjunctivitis is uncommon and data regarding treatment of gonococcal conjunctivitis among adults are limited, consultation with an infectious disease specialist should be considered.

### Recommended Regimen for Gonococcal Conjunctivitis Among Adolescents and Adults

Ceftriaxone 1 g IM in a single dose

Providers should consider one-time lavage of the infected eye with saline solution.

### Alternative Regimens

Cefotaxime 1 g IV every 8 hours

or

Ceftizoxime 1 g every 8 hours

If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

### Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infections, Management of Sex Partners).

### Disseminated Gonococcal Infection

Infrequently, *N. gonorrhoeae* can cause disseminated infection. Disseminated gonococcal infection (DGI) frequently results in petechial or pustular acral skin lesions, asymmetric polyarthralgia, tenosynovitis, or oligoarticular septic arthritis (899–901). Rarely, DGI is complicated by perihepatitis associated with gonococcal PID, endocarditis, or meningitis. Certain strains of *N. gonorrhoeae* that cause DGI can cause minimal genital inflammation, and urogenital or anorectal infections are often asymptomatic among DGI patients. If DGI is suspected, NAATs or culture specimens from all exposed urogenital and extragenital sites should be collected and processed, in addition to disseminated sites of infection (e.g., skin, synovial fluid, blood, or CSF). All *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility. Risk factors for dissemination have included female sex, menstruation, pregnancy, and terminal complement deficiency (899); however, reports are increasing among men (900,901). Persons receiving eculizumab, a monoclonal antibody that inhibits terminal complement activation, also might be at higher risk for DGI (902).

Hospitalization and consultation with an infectious disease specialist are recommended for initial therapy, especially for persons who might not comply with treatment, have an uncertain diagnosis, or have purulent synovial effusions or other complications. Examination for clinical evidence of endocarditis and meningitis should be performed.

### Treatment of Arthritis and Arthritis-Dermatitis Syndrome

#### Recommended Regimen for Gonococcal-Related Arthritis and Arthritis-Dermatitis Syndrome

Ceftriaxone 1 g IM or IV every 24 hours

If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

When treating for the arthritis-dermatitis syndrome, the provider can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of >7 days.

### Treatment of Gonococcal Meningitis and Endocarditis

#### Recommended Regimen for Gonococcal Meningitis and Endocarditis

Ceftriaxone 1–2 g IV every 24 hours

If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

No recent studies have been published regarding treatment of DGI involving the CNS or cardiovascular system. The duration of treatment for DGI in these situations has not been systematically studied and should be determined in consultation with an infectious disease specialist. Treatment for DGI should be guided by the results of antimicrobial susceptibility testing. Length of treatment should be determined based on clinical presentation. Therapy for meningitis should be continued with recommended parenteral therapy for 10–14 days. Parenteral antimicrobial therapy for endocarditis should be administered for >4 weeks. Treatment of gonococcal perihepatitis should be managed in accordance with the recommendations for PID in these guidelines.

### Management of Sex Partners

Gonococcal infection frequently is asymptomatic among sex partners of persons who have DGI. Providers should instruct patients to refer partners with whom they have had sexual contact during the previous 60 days for evaluation, testing, and presumptive treatment (see Gonococcal Infections, Management of Sex Partners).

### Gonococcal Infection Among Neonates

Prenatal screening and treatment of pregnant women for gonorrhea is the best method for preventing *N. gonorrhoeae* infection among neonates. Gonococcal infection among neonates results from perinatal exposure to the mother's infected cervix. It is usually an acute illness that manifests 2–5 days after birth. Prevalence of infection among neonates depends on the prevalence of infection among pregnant women and whether pregnant women are screened and treated for gonorrhea during

pregnancy. The most severe manifestations of *N. gonorrhoeae* infection among neonates are ophthalmia neonatorum and sepsis, which can include arthritis and meningitis. Less severe manifestations include rhinitis, vaginitis, urethritis, and scalp infection at sites of previous fetal monitoring.

### **Preventing Ophthalmia Neonatorum Caused by *N. gonorrhoeae***

Ocular prophylaxis and preventive gonorrhea screening and treatment of infected pregnant women are especially important because ophthalmia neonatorum can result in perforation of the globe of the eye and blindness (903). Ocular prophylaxis for gonococcal ophthalmia neonatorum has a long history of preventing sight-threatening gonococcal ocular infections. Cases in the United States are uncommon, which is likely attributable to gonorrhea screening programs for women, including pregnant women, that have contributed substantially to reduction in ophthalmia neonatorum (904). Neonatal ocular prophylaxis with erythromycin, the only agent available in the United States, is required by law in most states and is recommended because of safety, low cost, and ease of administration. It can contribute to preventing gonococcal blindness because not all pregnant women are screened for gonorrhea. The USPSTF recommends ocular prophylaxis with erythromycin ointment for all newborns <24 hours after birth (903). In addition to continuing routine ocular prophylaxis, prevention should focus on prenatal screening for *N. gonorrhoeae*, including

- screening pregnant women at risk (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, a sex partner who has an STI, or live in a community with high rates of gonorrhea) for *N. gonorrhoeae* infection at the first prenatal visit;
- treating all pregnant women with *N. gonorrhoeae* infection during pregnancy and retesting in 3 months, in the third trimester or at time of delivery (sex partners should be tested and treated);
- retesting pregnant women in the third trimester who initially tested negative but remained at increased risk for acquiring infection (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, a sex partner who has an STI, or live in a community with high rates of gonorrhea); and
- screening for gonorrhea at delivery for women not tested during pregnancy and at risk for infection (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, a sex partner who has an STI, or live

in a community with high rates of gonorrhea) or received no prenatal care; providers caring for the mother and the newborn should communicate to ensure follow-up on the results of laboratory tests performed at delivery, and if positive, prompt appropriate treatment of the newborn and mother.

Erythromycin is the only ophthalmic ointment recommended for use among neonates. Silver nitrate and tetracycline ophthalmic ointments are no longer manufactured in the United States, bacitracin is ineffective, and povidone iodine has not been studied adequately (905,906). Gentamicin ophthalmic ointment has been associated with severe ocular reactions (907,908). If erythromycin ointment is unavailable, infants at risk for exposure to *N. gonorrhoeae*, especially those born to a mother at risk for gonococcal infection or with no prenatal care, can be administered ceftriaxone 25–50 mg/kg body weight IV or IM, not to exceed 250 mg in a single dose.

#### **Recommended Regimen to Prevent Ophthalmia Neonatorum Caused by *N. gonorrhoeae***

**Erythromycin 0.5% ophthalmic ointment in each eye in a single application at birth**

Erythromycin ophthalmic ointment should be instilled into both eyes of neonates as soon as possible after delivery, regardless of whether they are delivered vaginally or by cesarean delivery. Ideally, ointment should be applied by using single-use tubes or ampules rather than multiple-use tubes. If prophylaxis is delayed (i.e., not administered in the delivery room), a monitoring system should be established to ensure that all newborns receive prophylaxis <24 hours after delivery.

### **Diagnostic Considerations**

Newborns at increased risk for gonococcal ophthalmia include those who did not receive ophthalmic prophylaxis and whose mothers had no prenatal care, have a history of STIs during pregnancy, or have a history of substance misuse. Gonococcal ophthalmia is strongly suspected when intracellular gram-negative diplococci are identified on Gram stain of conjunctival exudate, justifying presumptive treatment for gonorrhea after appropriate cultures and antimicrobial susceptibility testing for *N. gonorrhoeae* are performed. Presumptive treatment for *N. gonorrhoeae* might be indicated for newborns at increased risk for gonococcal ophthalmia who have increased WBCs (no GNID) in a Gram-stained smear of conjunctival exudate. Nongonococcal causes of neonatal ophthalmia include *Moraxella catarrhalis* and other *Neisseria* species, which are organisms that are indistinguishable from *N. gonorrhoeae* on Gram-stained smear but can be differentiated in the microbiology laboratory.

## Treatment of Gonococcal Ophthalmia Neonatorum

### Recommended Regimen for Gonococcal Ophthalmia Neonatorum

Ceftriaxone 25–50 mg/kg body weight IV or IM in a single dose, not to exceed 250 mg

One dose of ceftriaxone is adequate therapy for gonococcal ophthalmia. Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime 100 mg/kg body weight IV or IM as a single dose can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium. Topical antibiotic therapy alone is inadequate and unnecessary if systemic treatment is administered.

### Other Management Considerations

Chlamydial testing should be performed simultaneously from the inverted eyelid specimen (see Ophthalmia Neonatorum Caused by *C. trachomatis*). Newborns who have gonococcal ophthalmia should be evaluated for signs of disseminated infection (e.g., sepsis, arthritis, and meningitis). Newborns who have gonococcal ophthalmia should be managed in consultation with an infectious disease specialist.

### Management of Mothers and Their Sex Partners

Mothers of newborns with ophthalmia neonatorum caused by *N. gonorrhoeae* should be evaluated, tested, and presumptively treated for gonorrhea, along with their sex partners (see Gonococcal Infection Among Adolescents and Adults).

### Disseminated Gonococcal Infection and Gonococcal Scalp Abscesses Among Neonates

DGI might present as sepsis, arthritis, or meningitis and is a rare complication of neonatal gonococcal infection. Localized gonococcal infection of the scalp can result from fetal monitoring through scalp electrodes. Detecting gonococcal infection among neonates who have sepsis, arthritis, meningitis, or scalp abscesses requires cultures of blood, CSF, or joint aspirate. Specimens obtained from the conjunctiva, vagina, oropharynx, and rectum are useful for identifying the primary site or sites of infection. Antimicrobial susceptibility testing of all isolates should be performed. Positive Gram-stained smears of abscess exudate, CSF, or joint aspirate provide a presumptive basis for initiating treatment for *N. gonorrhoeae*.

## Treatment

### Recommended Regimens for Disseminated Gonococcal Infection Among Neonates

Ceftriaxone 25–50 mg/kg body weight/day IV or IM in a single daily dose for 7 days, with a duration of 10–14 days if meningitis is documented

or

Cefotaxime 25 mg/kg body weight/day IV or IM every 12 hours for 7 days, with a duration of 10–14 days if meningitis is documented

Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime 100 mg/kg body weight IV or IM as a single dose can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium.

### Other Management Considerations

Chlamydial testing should be performed simultaneously among neonates with gonococcal infection (see Chlamydial Infection Among Neonates). Neonates who have DGI should be managed in consultation with an infectious disease specialist.

### Management of Mothers and Their Sex Partners

Mothers of newborns who have DGI or scalp abscesses caused by *N. gonorrhoeae* should be evaluated, tested, and presumptively treated for gonorrhea, along with their sex partners (see Gonococcal Infection Among Adolescents and Adults).

### Neonates Born to Mothers Who Have Gonococcal Infection

Neonates born to mothers who have untreated gonorrhea are at high risk for infection. Neonates should be tested for gonorrhea at exposed sites (e.g., conjunctiva, vagina, rectum, and oropharynx) and treated presumptively for gonorrhea.

### Treatment in the Absence of Signs of Gonococcal Infection

### Recommended Regimen for Neonates Without Signs of Gonococcal Infection

Ceftriaxone 20–50 mg/kg body weight IV or IM in a single dose, not to exceed 250 mg

### Other Management Considerations

Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime 100 mg/kg body weight IV or IM as a single dose can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium. Age-appropriate chlamydial testing should be

performed simultaneously among neonates with gonococcal infection (see Chlamydial Infection Among Neonates). Follow-up examination is not required.

### Management of Mothers and Their Sex Partners

Mothers who have gonorrhea and their sex partners should be evaluated, tested, and presumptively treated for gonorrhea (see Gonococcal Infection Among Adolescents and Adults).

## Gonococcal Infection Among Infants and Children

Sexual abuse is the most frequent cause of gonococcal infection among infants and children (see Sexual Assault or Abuse of Children). For preadolescent girls, vaginitis is the most common manifestation of this infection; gonococcal-associated PID after vaginal infection can be less common among preadolescents than adults. Among sexually abused children, anorectal and pharyngeal infections with *N. gonorrhoeae* are frequently asymptomatic.

### Diagnostic Considerations

Culture can be used to test urogenital and extragenital sites for girls and boys. NAAT can be used to test for *N. gonorrhoeae* from vaginal and urine specimens from girls and urine for boys (see Sexual Assault or Abuse of Children). Although data regarding NAAT from extragenital sites (rectum and pharynx) among children are more limited, and performance is test dependent, no evidence supports that performance of NAAT for detection of *N. gonorrhoeae* among children differs from that among adults (553). Because of the implications of a *N. gonorrhoeae* diagnosis in a child, only validated FDA-cleared NAAT assays should be used with extragenital specimens. Consultation with an expert is necessary before using NAAT to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals (e.g., *N. meningitidis*, *Neisseria sicca*, *Neisseria lactamica*, *Neisseria cinerea*, or *M. catarrhalis*) and to ensure correct interpretation of results.

Gram stains are inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. If evidence of DGI exists, gonorrhea culture and antimicrobial susceptibility testing should be obtained from relevant clinical sites (see Disseminated Gonococcal Infection).

### Recommended Regimen for Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis Among Infants and Children Weighing ≤45 kg

Ceftriaxone 25–50 mg/kg body weight IV or IM in a single dose, not to exceed 250 mg IM

### Recommended Regimen for Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis Among Children Weighing >45 kg

Treat with the regimen recommended for adults (see Gonococcal Infections)

### Recommended Regimen for Bacteremia or Arthritis Among Children Weighing ≤45 kg

Ceftriaxone 50 mg/kg body weight (maximum dose: 2 g) IM or IV in a single dose daily every 24 hours for 7 days

### Recommended Regimen for Bacteremia or Arthritis Among Children Weighing >45 kg

Ceftriaxone 1 g IM or IV in a single dose daily every 24 hours for 7 days

### Other Management Considerations

Follow-up cultures are unnecessary. Only parenteral cephalosporins (i.e., ceftriaxone) are recommended for use among children. All children identified as having gonococcal infections should be tested for *C. trachomatis*, syphilis, and HIV (see Sexual Assault or Abuse of Children).

## *Mycoplasma genitalium*

*M. genitalium* causes symptomatic and asymptomatic urethritis among men and is the etiology of approximately 15%–20% of NGU, 20%–25% of nonchlamydial NGU, and 40% of persistent or recurrent urethritis (697,909,910). Infection with *C. trachomatis* is common in selected geographic areas (911–913), although *M. genitalium* is often the sole pathogen. Data are insufficient to implicate *M. genitalium* infection with chronic complications among men (e.g., epididymitis, prostatitis, or infertility). The consequences of asymptomatic infection with *M. genitalium* among men are unknown.

Among women, *M. genitalium* has been associated with cervicitis, PID, preterm delivery, spontaneous abortion, and infertility, with an approximately twofold increase in the risk for these outcomes among women infected with *M. genitalium* (766). *M. genitalium* infections among women are also frequently asymptomatic, and the consequences associated with asymptomatic *M. genitalium* infection are unknown.

*M. genitalium* can be detected among 10%–30% of women with clinical cervicitis (767,770,772,914–916). The existing evidence between *M. genitalium* and cervicitis is mostly supportive of a causal association. Elevated proinflammatory cytokines have been demonstrated among women with *M. genitalium*, with return to baseline levels after clearance of the pathogen (917).

*M. genitalium* is identified in the cervix or endometrium of women with PID more often than in women without PID (918–924). Prevalence of *M. genitalium* among women with PID ranges from 4% to 22% (925,926) and was reported as 60% in one study of women with postabortal PID (918). The association with PID is supported by early studies among nonhuman primates that determined that endosalpingitis develops after inoculation with *M. genitalium* (927). Recent studies evaluating the lower and upper genital tract using highly sensitive *M. genitalium* NAAT assays or the role of *M. genitalium* in histologically defined endometritis have reported significantly elevated risk for PID (928). However, most studies of *M. genitalium* and PID, even those that controlled extensively for other infections and behavioral and biologic risk, are cross-sectional. The few prospective studies that have evaluated the role of *M. genitalium* in establishing subsequent PID demonstrated increased PID risk; however, these were not statistically significant associations, often because of a lack of statistical power. No clinical trial data are available that demonstrate that treating *M. genitalium* cervical infection prevents development of PID or endometritis. Although data regarding the benefits of testing women with PID for *M. genitalium* and the importance of directing treatment against this organism are limited, the associations of *M. genitalium* with cervicitis and PID in cross-sectional studies using NAAT testing are consistent (928).

Data from case-control serologic studies (929–931) and a meta-analysis of clinical studies (766) indicate a potential role in causing infertility. However, seroassays are suboptimal and inconclusive. Similarly, evidence for a role for *M. genitalium* infection during pregnancy as a cause of perinatal complications, including preterm delivery, spontaneous abortion, or low birthweight, are conflicting because evidence is insufficient to attribute cause (766,932–934). Data are limited regarding ectopic pregnancy and neonatal *M. genitalium* infection (935,936).

Rectal infection with *M. genitalium* has been reported among 1%–26% of MSM (937–940) and among 3% of women (941). Rectal infections often are asymptomatic, although higher prevalence of *M. genitalium* has been reported among men with rectal symptoms. Similarly, although asymptomatic *M. genitalium* has been detected in the pharynx, no evidence exists of it causing oropharyngeal symptoms or systemic disease.

Urogenital *M. genitalium* infection is associated with HIV among both men and women (942–944); however, the data are from case-control and cross-sectional studies. Risk for HIV infection is increased among women with *M. genitalium*, and evidence indicates that HIV shedding occurs more often among persons with *M. genitalium* and HIV infection who are not taking ART than among persons without *M. genitalium* (942,944).

## Antimicrobial Resistance

Resistance to azithromycin has been rapidly increasing and has been confirmed in multiple studies. Prevalence of molecular markers for macrolide resistance, which highly correlates with treatment failure, ranges from 44% to 90% in the United States, Canada, Western Europe, and Australia (697,702,945–953). Treatment with azithromycin alone has been reported to select for resistance (705,954,955), with treatment of macrolide-susceptible infections with a 1-g dose of azithromycin resulting in selection of resistant-strain populations in 10%–12% of cases. The prevalence of quinolone resistance markers is much lower (697,956–959). The first clinical treatment failures after moxifloxacin were associated specifically with the S83I mutation in the *parC* gene (954,960). Prevalence of the S83I mutation in the United States ranges from 0% to 15% (947); however, correlation with fluoroquinolone treatment failure is less consistent than that with mutations associated with macrolide resistance (953,961,962). Clinically relevant quinolone resistance often is associated with coexistent macrolide resistance (954).

## Diagnostic Considerations

*M. genitalium* is an extremely slow-growing organism. Culture can take up to 6 months, and technical laboratory capacity is limited to research settings. NAAT for *M. genitalium* is FDA cleared for use with urine and urethral, penile meatal, endocervical, and vaginal swab samples (<https://www.hologic.com/package-inserts/diagnostic-products/aptima-mycoplasma-genitalium-assay>). Molecular tests for macrolide (i.e., azithromycin) or quinolone (i.e., moxifloxacin) resistance markers are not commercially available in the United States. However, molecular assays that incorporate detection of mutations associated with macrolide resistance are under evaluation.

Men with recurrent NGU should be tested for *M. genitalium* using an FDA-cleared NAAT. If resistance testing is available, it should be performed and the results used to guide therapy. Women with recurrent cervicitis should be tested for *M. genitalium*, and testing should be considered among women with PID. Testing should be accompanied with resistance testing, if available. Screening of asymptomatic *M. genitalium* infection among women and men or extragenital testing for *M. genitalium* is not recommended. In clinical practice, if testing is unavailable, *M. genitalium* should be suspected in cases of persistent or recurrent urethritis or cervicitis and considered for PID.

## Treatment

*M. genitalium* lacks a cell wall, and thus antibiotics targeting cell-wall biosynthesis (e.g.,  $\beta$ -lactams including penicillins and cephalosporins) are ineffective against this organism. Because of the high rates of macrolide resistance with treatment failures (707) and efficient selection of additional resistance, a 1-g dose of azithromycin should not be used.

Two-stage therapy approaches, ideally using resistance-guided therapy, are recommended for treatment. Resistance-guided therapy has demonstrated cure rates of >90% and should be used whenever possible (759,963); however, it requires access to macrolide-resistance testing. As part of this approach, doxycycline is provided as initial empiric therapy, which reduces the organism load and facilitates organism clearance, followed by macrolide-sensitive *M. genitalium* infections treated with high-dose azithromycin; macrolide-resistant infections are treated with moxifloxacin (964,965).

### Recommended Regimens if *M. genitalium* Resistance Testing Is Available

If macrolide sensitive: Doxycycline 100 mg orally 2 times/day for 7 days, followed by azithromycin 1 g orally initial dose, followed by 500 mg orally once daily for 3 additional days (2.5 g total)

If macrolide resistant: Doxycycline 100 mg orally 2 times/day for 7 days followed by moxifloxacin 400 mg orally once daily for 7 days

### Recommended Regimen if *M. genitalium* Resistance Testing Is Not Available

If *M. genitalium* is detected by an FDA-cleared NAAT: Doxycycline 100 mg orally 2 times/day for 7 days, followed by moxifloxacin 400 mg orally once daily for 7 days

Although the majority of *M. genitalium* strains are sensitive to moxifloxacin, resistance has been reported, and adverse side effects and cost should be considered with this regimen. In settings without access to resistance testing and when moxifloxacin cannot be used, an alternative regimen can be considered, based on limited data: doxycycline 100 mg orally 2 times/day for 7 days, followed by azithromycin (1 g orally on day 1 followed by 500 mg once daily for 3 days) and a test of cure 21 days after completion of therapy (963). Because of the high prevalence of macrolide resistance and high likelihood of treatment failure, this regimen should be used only when a test of cure is possible, and no other alternatives exist. If symptomatic treatment failure or a positive test of cure occurs after this regimen, expert consultation is recommended. Data are limited regarding use of minocycline in instances of treatment failure (966).

Recommended PID treatment regimens are not effective against *M. genitalium*. Initial empiric therapy for PID, which includes doxycycline 100 mg orally 2 times/day for 14 days, should be provided at the time of presentation for care. If

*M. genitalium* is detected, a regimen of moxifloxacin 400 mg orally once daily for 14 days has been effective in eradicating the organism. Nevertheless, no data have been published that assess the benefits of testing women with PID for *M. genitalium*, and the importance of directing treatment against this organism is unknown.

## Follow-Up

Test of cure is not recommended for asymptomatic persons who received treatment with a recommended regimen. In settings in which *M. genitalium* testing is available, persons with persistent urethritis, cervicitis, or PID accompanied by detection of *M. genitalium* should be treated with moxifloxacin.

## Management of Sex Partners

Recent studies report a high concordance of *M. genitalium* among partners of males, females, and MSM; however, no studies have determined whether reinfection is reduced with partner treatment (940,967,968). Sex partners of patients with symptomatic *M. genitalium* infection can be tested, and those with a positive test can be treated to possibly reduce the risk for reinfection. If testing the partner is not possible, the antimicrobial regimen that was provided to the patient can be provided.

## Special Considerations

### HIV Infection

Persons who have *M. genitalium* and HIV infection should receive the same treatment regimen as those persons without HIV.

## Diseases Characterized by Vulvovaginal Itching, Burning, Irritation, Odor, or Discharge

The majority of women will have a vaginal infection, characterized by discharge, itching, burning, or odor, during their lifetime. With the availability of complementary and alternative therapies and over-the-counter medications for candidiasis, symptomatic women often seek these products before or in addition to an evaluation by a medical provider.

Obtaining a medical history alone has been reported to be insufficient for accurate diagnosis of vaginitis and can lead to inappropriate administration of medication (969). Therefore, a careful history, examination, and laboratory testing to determine the etiology of any vaginal symptoms are warranted. Information regarding sexual behaviors and

practices, sex of sex partners, menses, vaginal hygiene practices (e.g., douching), and self-treatment with oral and intravaginal medications or other products should be elicited. The infections most frequently associated with vaginal symptoms are BV (i.e., replacement of the vaginal flora by an overgrowth of anaerobic bacteria including *G. vaginalis*, *Prevotella bivia*, *A. vaginae*, *Megasphaera* type 1, and numerous other fastidious or uncultivated anaerobes), trichomoniasis, and vulvovaginal candidiasis (VVC). Cervicitis can also cause an abnormal vaginal discharge. Although VVC is usually not sexually transmitted, it is included in this section because it is frequently diagnosed among women who have vaginal symptoms or are being evaluated for an STI.

Multiple diagnostic methods are available for identifying the etiology of vaginal symptoms. Clinical laboratory testing can identify the vaginitis cause in the majority of women and is discussed in detail in the sections of this report dedicated to each condition. In the clinician's office, the cause of vaginal symptoms can often be determined by pH, a potassium hydroxide (KOH) test, and microscopic examination of a wet mount of fresh samples of vaginal discharge. The pH of the vaginal secretions can be measured by pH paper; an elevated pH (i.e., >4.5) is common with BV or trichomoniasis (although trichomoniasis can also be present with a normal vaginal pH). Because pH testing is not highly specific, vaginal discharge should be further examined microscopically by first diluting one sample in 1 or 2 drops of 0.9% normal saline solution on one slide and a second sample in 10% KOH solution (samples that emit an amine odor immediately upon application of KOH suggest BV or trichomoniasis). Coverslips are then placed on the slides, and they are examined under a microscope at low and high power. The saline-solution specimen might display motile trichomonads or clue cells (i.e., epithelial cells with borders obscured by small anaerobic bacteria), which are characteristic of BV. The KOH specimen typically is used to identify hyphae or blastospores observed with candidiasis. However, absence of trichomonads in saline or fungal elements in KOH samples does not rule out these infections because the sensitivity of microscopy is approximately 50% compared with NAAT (trichomoniasis) or culture (yeast) (670). Presence of WBCs without evidence of trichomonads or yeast might also indicate cervicitis (see Cervicitis).

In settings where pH paper, KOH, and microscopy are unavailable, a broad range of clinical laboratory tests, described in the diagnosis section for each disease, can be used. Presence of objective signs of vulvovaginal inflammation in the absence of vaginal pathogens after laboratory testing indicates the possibility of mechanical, chemical, allergic, or

other noninfectious causes of vulvovaginal signs or symptoms. For women with persistent symptoms and no clear etiology, referral to a specialist should be considered.

## Bacterial Vaginosis

BV is a vaginal dysbiosis resulting from replacement of normal hydrogen peroxide and lactic-acid-producing *Lactobacillus* species in the vagina with high concentrations of anaerobic bacteria, including *G. vaginalis*, *Prevotella* species, *Mobiluncus* species, *A. vaginae*, and other BV-associated bacteria. A notable feature is the appearance of a polymicrobial biofilm on vaginal epithelial cells (970). Certain women experience transient vaginal microbial changes, whereas others experience them for longer intervals (971). BV is a highly prevalent condition and the most common cause of vaginal discharge worldwide (972). However, in a nationally representative survey, the majority of women with BV were asymptomatic (310).

BV is associated with having multiple male sex partners, female partners, sexual relationships with more than one person (973), a new sex partner, lack of condom use (974), douching (975,976), and HSV-2 seropositivity (977). Male circumcision reduces the risk for BV among women (978). In addition, BV prevalence increases during menses (979,980). Women who have never been sexually active are rarely affected (981). The cause of the microbial alteration that precipitates BV is not fully understood, and whether BV results from acquisition of a single sexually transmitted pathogen is unknown. BV prevalence has been reported to increase among women with copper-containing IUDs (972,982). Hormonal contraception does not increase risk for BV (983) and might protect against BV development (983,984). Vitamin D deficiency has not been reported to be a risk factor for BV (985).

Women with BV are at increased risk for STI acquisition, such as HIV, *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* (977), *M. genitalium* (986), HPV (987), and HSV-2 (988); complications after gynecologic surgery; complications of pregnancy; and recurrence of BV (971,989–991). BV also increases HIV infection acquisition (992) because specific BV-associated bacteria can increase susceptibility to HIV (993,994) and the risk for HIV transmission to male sex partners (187). Evaluation of short-term valacyclovir suppression among women with HSV-2 did not decrease the risk for BV, despite effective suppression of HSV-2 (995).

Although BV-associated bacteria can be identified on male genitalia (996,997), treatment of male sex partners has not been beneficial in preventing the recurrence of BV (998). Among WSW, a high level of BV concordance occurs between sex partners (292); however, no studies have evaluated treatment of female sex partners of WSW to prevent BV recurrence.

## Diagnostic Considerations

BV can be diagnosed by using clinical criteria (i.e., Amsel's diagnostic criteria) (999) or by determining the Nugent score from a vaginal Gram stain (1000). Vaginal Gram stain, considered the reference standard laboratory method for diagnosing BV, is used to determine the relative concentration of lactobacilli (i.e., long gram-positive rods), small gram-negative and gram-variable rods (i.e., *G. vaginalis* or *Bacteroides*), and curved gram-negative rods (i.e., *Mobiluncus*) characteristic of BV. A Nugent score of 0–3 is consistent with a *Lactobacillus*-predominant vaginal microbiota, 4–6 with intermediate microbiota (emergence of *G. vaginalis*), and 7–10 with BV. Clinical diagnosis of BV by Amsel criteria requires at least three of the following four symptoms or signs:

- Homogeneous, thin discharge (milklike consistency) that smoothly coats the vaginal walls
- Clue cells (e.g., vaginal epithelial cells studded with adherent bacteria) on microscopic examination
- pH of vaginal fluid >4.5
- A fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test)

Detection of at least three Amsel criteria has been correlated with results by Gram stain (1001). The sensitivity and specificity of the Amsel criteria are 37%–70% and 94%–99%, respectively, compared with the Nugent score (1002).

In addition to the Amsel criteria, multiple POC tests are available for BV diagnosis. The Osom BV Blue test (Sekisui Diagnostics) detects vaginal sialidase activity (1003,1004). The Affirm VP III (Becton Dickinson) is an oligonucleotide probe test that detects high concentrations of *G. vaginalis* nucleic acids ( $>5 \times 10^5$  CFU of *G. vaginalis*/mL of vaginal fluid) for diagnosing BV, *Candida* species, and *T. vaginalis*. This test has been reported to be most useful for symptomatic women in conjunction with vaginal pH measurement and presence of amine odor (sensitivity of 97%); specificity is 81% compared with Nugent. Finally, the FemExam Test Card (Cooper Surgical) measures vaginal pH, presence of trimethylamine (a metabolic by-product of *G. vaginalis*), and proline aminopeptidase (1005). Sensitivity is 91% and specificity is 61%, compared with Nugent. This test has primarily been studied in resource-poor settings (1005), and although it has been reported to be beneficial compared with syndromic management, it is not a preferred diagnostic method for BV diagnosis.

Multiple BV NAATs are available for BV diagnosis among symptomatic women (1002). These tests are based on detection of specific bacterial nucleic acids and have high sensitivity and specificity for BV (i.e., *G. vaginalis*, *A. vaginae*, BVAB2, or *Megasphaera* type 1) (1006) and certain lactobacilli (i.e.,

*Lactobacillus crispatus*, *Lactobacillus jensenii*, and *Lactobacillus gasseri*). They can be performed on either clinician- or self-collected vaginal specimens with results available in <24 hours, depending on the availability of the molecular diagnostic platform (1002). Five quantitative multiplex PCR assays are available: Max Vaginal Panel (Becton Dickinson) (1007), Aptima BV (Hologic), NuSwab VG (LabCorp) (1008), OneSwab BV Panel PCR with Lactobacillus Profiling by qPCR (Medical Diagnostic Laboratories) (1009), and SureSwab BV (Quest Diagnostics). Two of these assays are FDA cleared (BD Max Vaginal Panel and Aptima BV), and the other three are laboratory-developed tests.

The Max Vaginal Panel provides results by an algorithmic analysis of molecular DNA detection of *Lactobacillus* species (*L. crispatus* and *L. jensenii*) in addition to *G. vaginalis*, *A. vaginae*, BVAB2, and *Megasphaera* type 1. This test has 90.5% sensitivity and 85.8% specificity for BV diagnosis, compared with Amsel criteria and Nugent score. It also provides results for *Candida* species and *T. vaginalis*. The Aptima BV detects *G. vaginalis*, *A. vaginae*, and certain *Lactobacillus* species including *L. crispatus*, *L. jensenii*, and *L. gasseri*, with sensitivity and specificity ranging from 95.0% to 97.3% and 85.8% to 89.6%, respectively (using either clinician- or patient-collected vaginal swabs). The three laboratory-developed tests (NuSwab VG, OneSwab BV Panel PCR with Lactobacillus Profiling by qPCR, and SureSwab BV) have to be internally validated before use for patient care yet have good sensitivity and specificity, similar to FDA-cleared assays. BV NAATs should be used among symptomatic women only (e.g., women with vaginal discharge, odor, or itch) because their accuracy is not well defined for asymptomatic women. Despite the availability of BV NAATs, traditional methods of BV diagnosis, including the Amsel criteria, Nugent score, and the Affirm VP III assay, remain useful for diagnosing symptomatic BV because of their lower cost and ability to provide a rapid diagnosis. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for diagnosing BV because of their low sensitivity and specificity.

## Treatment

Treatment for BV is recommended for women with symptoms. Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection. Other potential benefits of treatment include reduction in the risk for acquiring *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2 (971,986–988,990,1010). No data are available that directly compare the efficacy of oral and topical medications for treating BV.

**Recommended Regimens for Bacterial Vaginosis**

- Metronidazole** 500 mg orally 2 times/day for 7 days  
*or*  
**Metronidazole gel** 0.75% one full applicator (5 g) intravaginally, once daily for 5 days  
*or*  
**Clindamycin cream** 2% one full applicator (5 g) intravaginally at bedtime for 7 days

A review regarding alcohol consumption during metronidazole treatment reported no in vitro studies, animal models, reports of adverse effects, or clinical studies providing convincing evidence of a disulfiram-like interaction between alcohol and metronidazole (1011). The previous warning against simultaneous use of alcohol and metronidazole was based on laboratory experiments and individual case histories in which the reported reactions were equally likely to have been caused by alcohol alone or by adverse effects of metronidazole.

Metronidazole does not inhibit acetaldehyde dehydrogenase, as occurs with disulfiram. Ethanol alone or ethanol-independent side effects of metronidazole might explain the suspicion of disulfiram-like effects. Thus, refraining from alcohol use while taking metronidazole (or tinidazole) is unnecessary. Clindamycin cream is oil based and might weaken latex condoms and diaphragms for 5 days after use (refer to clindamycin product labeling for additional information).

Women should be advised to refrain from sexual activity or to use condoms consistently and correctly during the BV treatment regimen. Douching might increase the risk for relapse, and no data support use of douching for treatment or symptom relief.

**Alternative Regimens**

- Clindamycin** 300 mg orally 2 times/day for 7 days  
*or*  
**Clindamycin ovules** 100 mg intravaginally once at bedtime for 3 days\*  
*or*  
**Secnidazole** 2 g oral granules in a single dose†  
*or*  
**Tinidazole** 2 g orally once daily for 2 days  
*or*  
**Tinidazole** 1 g orally once daily for 5 days

\* Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended.

† Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing.

Alternative regimens include secnidazole oral granules (1012–1014), multiple oral tinidazole regimens (1015), or clindamycin (oral or intravaginal) (1016). In a phase 3 clinical trial of secnidazole 2 g oral granules versus placebo, BV clinical cure rates at days 21–30 were 53% in the secnidazole

arm compared with 19% in the placebo arm ( $p < 0.001$ ) (1013). Secnidazole is listed as an alternative regimen, due to its higher cost and lack of long-term outcomes compared with recommended BV treatments. A patient savings card for secnidazole is available at <https://www.solosec.com/savings-card>.

Additional BV treatment regimens include metronidazole 1.3% vaginal gel in a single dose (1017,1018) and clindamycin phosphate (Clindesse) 2% vaginal cream in a single dose (1019). In a phase 3 clinical trial of metronidazole 1.3% vaginal gel versus placebo, BV clinical cure rates at day 21 were 37.2% in the metronidazole 1.3% vaginal gel arm, compared with 26.6% in the placebo arm ( $p = 0.01$ ) (1018). A patient savings card for metronidazole 1.3% vaginal gel is available at [https://nuvessa.com/nuvessa\\_files/19\\_Nuvessa\\_WEB\\_Card\\_032819.pdf](https://nuvessa.com/nuvessa_files/19_Nuvessa_WEB_Card_032819.pdf). In a multicenter, randomized, single-blind, parallel-group study of Clindesse 2% vaginal cream single dose versus clindamycin 2% vaginal cream at bedtime for 7 days among 540 women with BV, no statistically significant difference existed between groups in clinical cure at days 21–30 (64.3% versus 63.2%;  $p = 0.95$ ) (1019); however, this study had methodologic problems. A patient savings card for Clindesse 2% vaginal cream is available at [https://www.clindesse.com/pdf/CLINDESSE\\_SavingsCard.pdf](https://www.clindesse.com/pdf/CLINDESSE_SavingsCard.pdf).

BV biofilm disrupting agents (i.e., TOL-463) (1020) are being investigated to determine their role in enhancing the likelihood of BV cure relative to approved therapies. Studies have evaluated the clinical and microbiologic efficacy of intravaginal *Lactobacillus* and other probiotic formulations to treat BV and restore normal vaginal microbiota (1021–1025); overall, no studies support these products as an adjunctive or replacement therapy for women with BV.

**Other Management Considerations**

All women with BV should be tested for HIV and other STIs.

**Follow-Up**

Follow-up visits are unnecessary if symptoms resolve. Because persistent or recurrent BV is common, women should be advised to return for evaluation if symptoms recur. Limited data are available regarding optimal management strategies for women with persistent or recurrent BV. Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence (1026). For women with multiple recurrences after completion of a recommended regimen, either 0.75% metronidazole gel or 750 mg metronidazole vaginal suppository twice weekly for >3 months has been reported to reduce recurrences, although this benefit does not

persist when suppressive therapy is discontinued (1027,1028). Limited data indicate that for women with multiple recurrences, an oral nitroimidazole (metronidazole or tinidazole 500 mg 2 times/day for 7 days), followed by intravaginal boric acid 600 mg daily for 21 days and suppressive 0.75% metronidazole gel twice weekly for 4–6 months, might be an option for women with recurrent BV (1029). Monthly oral metronidazole 2 g administered with fluconazole 150 mg has also been evaluated as suppressive therapy; this regimen reduced the BV incidence and promoted colonization with normal vaginal microbiota (1030). A randomized controlled trial of a dendrimer-based microbicide 1% vaginal gel (Astodrimer) also reported favorable results in prolonging the time to BV recurrence, compared with placebo (1031). In addition, a clinical trial of *L. crispatus* CTV-05 (Lactin-V), administered vaginally in 4 consecutive daily doses for 4 days in week 1 followed by twice weekly doses for 10 weeks (after initial treatment with 5 days of 0.75% vaginal metronidazole gel), reported a substantially lower incidence of BV recurrence at 12 weeks in the Lactin-V arm, compared with placebo (1032); however this medication is not yet FDA cleared or commercially available. High-dose Vitamin D supplementation has not been determined to decrease BV recurrence in randomized controlled trials (1033) and is not recommended.

### Management of Sex Partners

Data from earlier clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner (998). Therefore, routine treatment of sex partners is not recommended. However, a pilot study reported that male partner treatment (i.e., metronidazole 400 mg orally 2 times/day in conjunction with 2% clindamycin cream applied topically to the penile skin 2 times/day for 7 days) of women with recurrent BV had an immediate and sustained effect on the composition of the vaginal microbiota, with an overall decrease in bacterial diversity at day 28 (1034). Male partner treatment also had an immediate effect on the composition of the penile microbiota; however, this was not as pronounced at day 28, compared with that among women. A phase 3 multicenter randomized double-blinded trial evaluating the efficacy of a 7-day oral metronidazole regimen versus placebo for treatment of male sex partners of women with recurrent BV did not find that male partner treatment reduced BV recurrence in female partners, although women whose male partners adhered to multidose metronidazole were less likely to experience treatment failure (1035).

## Special Considerations

### Drug Allergy, Intolerance, or Adverse Reactions

Intravaginal clindamycin cream is preferred in case of allergy or intolerance to metronidazole or tinidazole. Intravaginal metronidazole gel can be considered for women who are not allergic to metronidazole but do not tolerate oral metronidazole.

### Pregnancy

BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis (989,991,1036). Studies have been undertaken to determine the efficacy of BV treatment among this population, including two trials demonstrating that oral metronidazole was efficacious during pregnancy by using the 250 mg 3 times/day regimen (1037,1038); however, oral metronidazole administered as a 500 mg 2 times/day regimen can also be used. One trial involving a limited number of participants revealed treatment with oral metronidazole 500 mg 2 times/day for 7 days to be equally effective as metronidazole gel 0.75% for 5 days, with cure rates of 70% by using Amsel criteria to define cure (1039). Another trial demonstrated a cure rate of 85% by using Gram-stain criteria after treatment with oral clindamycin 300 mg 2 times/day for 7 days (1040–1043).

Although older studies indicated a possible link between using vaginal clindamycin during pregnancy and adverse outcomes for the newborn, newer data demonstrate that this treatment approach is safe for pregnant women (1044). Although metronidazole crosses the placenta, no evidence of teratogenicity or mutagenic effects among infants has been reported in multiple cross-sectional, case-control, and cohort studies of pregnant women (1041–1043). These data indicate that metronidazole therapy poses low risk during pregnancy. Data from human studies are limited regarding the use of tinidazole in pregnancy; however, animal data demonstrate that such therapy poses moderate risk. Thus, tinidazole should be avoided during pregnancy (431). Data are insufficient regarding efficacy and adverse effects of secnidazole, Clindesse 2% vaginal cream, metronidazole 1.3% vaginal gel, and 750-mg vaginal metronidazole tablets during pregnancy; thus, their use should be avoided.

Oral therapy has not been reported to be superior to topical therapy for treating symptomatic BV in effecting cure or preventing adverse outcomes of pregnancy. Pregnant women can be treated with any of the recommended regimens for nonpregnant women, in addition to the alternative regimens of oral clindamycin and clindamycin ovules.

Treatment of asymptomatic BV among pregnant women at high risk for preterm delivery (i.e., those with a previous preterm birth or late miscarriage) has been evaluated by multiple studies, which have yielded mixed results. Seven trials have evaluated treatment of pregnant women with asymptomatic BV at high risk for preterm delivery: one revealed harm (1045), two reported no benefit (1046,1047), and four demonstrated benefit (1037,1038,1048,1049).

Treatment of asymptomatic BV among pregnant women at low risk for preterm delivery has not been reported to reduce adverse outcomes of pregnancy in a large multicenter randomized controlled trial (1050). Therefore, routine screening for BV among asymptomatic pregnant women at high or low risk for preterm delivery for preventing preterm birth is not recommended.

Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are less than those used to treat infections among infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable but remain less than maternal plasma levels (<https://www.ncbi.nlm.nih.gov/books/NBK501922/?report=classic>). Although multiple reported case series identified no evidence of metronidazole-associated adverse effects for breastfed infants, certain clinicians recommend deferring breastfeeding for 12–24 hours after maternal treatment with a single 2-g dose of metronidazole (1051). Lower doses produce a lower concentration in breast milk and are considered compatible with breastfeeding (1052,1053).

## HIV Infection

BV appears to recur with higher frequency among women who have HIV infection (1054). Women with HIV infection and BV should receive the same treatment regimen as those who do not have HIV.

## Trichomoniasis

Trichomoniasis is estimated to be the most prevalent nonviral STI worldwide, affecting approximately 3.7 million persons in the United States (838,1055). Because trichomoniasis is not a reportable disease (1056), and no recommendations are available for general screening for *T. vaginalis*, the epidemiology of trichomoniasis has largely come from population-based and clinic-based surveillance studies. The U.S. population-based *T. vaginalis* prevalence is 2.1% among females and 0.5% among males, with the highest rates among Black females (9.6%) and Black males (3.6%), compared with non-Hispanic White women (0.8%) and Hispanic women (1.4%) (1057,1058). Unlike chlamydia and gonorrhea, *T. vaginalis* prevalence

rates are as high among women aged >24 years as they are for women aged <24 years (1057). Among persons attending nine geographically diverse STD clinics, the trichomonas prevalence was 14.6% among women (1059), and a study of STD clinic attendees in Birmingham, Alabama, identified a prevalence of 27% among women and 9.8% among men (1060). Symptomatic women have a four times higher rate of infection than asymptomatic women (26% versus 6.5%) (1061). Rates are also high among incarcerated persons of both sexes at 9%–32% of incarcerated women (386,387,391,392,1062) and 3.2%–8% of incarcerated men (388). Women with a history of incarceration are two to five times more likely to have *T. vaginalis* (387,388,1063,1064). Other risk factors for *T. vaginalis* include having two or more sex partners during the previous year, having less than a high school education, and living below the national poverty level (1065). Women with BV are at higher risk for *T. vaginalis* (1066). Male partners of women with trichomoniasis are likely to have infection (1067), although the prevalence of trichomoniasis among MSM is low (179,1068).

The majority of persons who have trichomoniasis (70%–85%) either have minimal or no genital symptoms, and untreated infections might last from months to years (137,1069,1070). Men with trichomoniasis sometimes have symptoms of urethritis, epididymitis, or prostatitis, and women with trichomoniasis sometimes have vaginal discharge, which can be diffuse, malodorous, or yellow-green with or without vulvar irritation, and might have a strawberry-appearing cervix, which is observed more often on colposcopy than on physical examination (1071). Although many persons might be unaware of their infection, it is readily passed between sex partners during penile-vaginal sex (1072) or through transmission of infected vaginal fluids or fomites among women who have sex with women (275,294).

Among persons who are sexually active, the best way to prevent genital trichomoniasis is through consistent and correct use of condoms (external or internal) (18). Partners of men who have been circumcised might have a somewhat reduced risk for *T. vaginalis* infection (1072,1073). Douching is not recommended because it might increase the risk for vaginal infections, including trichomoniasis (1074).

*T. vaginalis* causes reproductive morbidity and has been reported to be associated with a 1.4-times greater likelihood of preterm birth, premature rupture of membranes, and infants who are small for gestational age (1075). *T. vaginalis* was also determined to be associated with a 2.1-fold increased risk for cervical cancer in a meta-analysis (1076). Another meta-analysis of six studies reported a slightly elevated but not statistically significant association between *T. vaginalis* and prostate cancer (1077).

*T. vaginalis* infection is associated with a 1.5-fold increased risk for HIV acquisition and is associated with an increase in HIV vaginal shedding, which is reduced with *T. vaginalis* treatment among women without viral suppression (1078,1079). Among women with HIV infection, *T. vaginalis* infection is associated with increased risk for PID (1080–1082).

Diagnostic testing for *T. vaginalis* should be performed for women seeking care for vaginal discharge. Annual screening might be considered for persons receiving care in high-prevalence settings (e.g., STD clinics and correctional facilities) and for asymptomatic women at high risk for infection (e.g., multiple sex partners, transactional sex, drug misuse, or a history of STIs or incarceration). However, data are lacking regarding whether screening and treatment for asymptomatic trichomoniasis in high-prevalence settings for women at high risk can reduce any adverse health events and health disparities or reduce community infection burden. Decisions about screening can be guided by local epidemiology of *T. vaginalis* infection. Routine annual screening for *T. vaginalis* among asymptomatic women with HIV infection is recommended because of these adverse events associated with trichomoniasis and HIV infection.

Extragenital *T. vaginalis* is possible but highly uncommon compared with genital infections. A study of 500 men in San Francisco, California, reported a 0.6% rate of rectal *T. vaginalis* (1083); however, this might reflect deposition of *T. vaginalis* DNA and not necessarily active infection. Few studies of extragenital *T. vaginalis* among women have been published. The efficacy, benefit, and cost-effectiveness of extragenital screening are unknown, and no tests are FDA cleared for extragenital testing; therefore, rectal and oral testing for *T. vaginalis* is not recommended.

## Diagnostic Considerations

Wet-mount microscopy traditionally has been used as the preferred diagnostic test for *T. vaginalis* among women because it is inexpensive and can be performed at the POC; however, it has low sensitivity (44%–68%) compared with culture (1084–1086). To improve detection, clinicians using wet mounts should attempt to evaluate slides immediately after specimen collection because sensitivity decreases quickly to 20% within 1 hour after collection (1087). More highly sensitive and specific molecular diagnostic options are available, which should be used in conjunction with a negative wet mount when possible.

NAATs are highly sensitive, detecting more *T. vaginalis* infections than wet-mount microscopy among women (1060). The Aptima *T. vaginalis* assay (Becton Dickinson) is FDA cleared for detection of *T. vaginalis* from symptomatic or asymptomatic women. Reliable samples include

clinician-collected endocervical swabs, clinician-collected vaginal swabs, female urine specimens, and liquid Pap smear specimens collected in PreservCyt Solution (Hologic) (698,1088). This assay detects RNA by transcription-mediated amplification with a sensitivity of 95.3%–100% and specificity of 95.2%–100%, compared with wet mount and culture (1088,1089). Among women, vaginal swabs and urine specimens have <100% concordance (1084). This assay has not been FDA cleared for use among men and should be internally validated in accordance with CLIA regulations before use with urine or urethral swabs from men. The Probe Tec TV Q<sup>x</sup> Amplified DNA Assay (Becton Dickinson) is FDA cleared for detection of *T. vaginalis* from vaginal (patient-collected or clinician-collected) swabs, endocervical swabs, or urine specimens from women and has sensitivity of 98.3% and specificity of 99.6%, compared with wet mount and culture (1090). Similar to the Aptima *T. vaginalis* assay, this test is only FDA cleared for use among women and should be internally validated for use with men. The Max CTGCTV2 assay (Becton Dickinson) is also FDA cleared for detection of *T. vaginalis* in patient-collected or clinician-collected vaginal swab specimens and male and female urine specimens, with sensitivity and specificity of 96.2%–100% and 99.1%–100%, respectively, depending on the specimen type, compared with wet mount and culture (1091). GeneXpert TV (Cepheid) is a moderately complex rapid test that can be performed in ≤1 hour and can be used at the POC (1092). It has been FDA cleared for use with female urine specimens, endocervical swabs, patient-collected or clinician-collected vaginal specimens, and male urine specimens, with sensitivity and specificity of 99.5%–100% and 99.4%–99.9% (1007), respectively, compared with wet mount and culture.

Multiple FDA-cleared rapid tests are available for detecting *T. vaginalis* with improved sensitivities and specificities, compared with wet mount. The Osom trichomonas rapid test (Sekisui Diagnostics) is an antigen-detection test that uses immunochromatographic capillary flow dipstick technology that can be performed at the POC by using clinician-obtained vaginal specimens. Results are available in approximately 10–15 minutes, with sensitivities of 82%–95% and specificity of 97%–100%, compared with wet mount, culture, and transcription-mediated amplification (1089,1093,1094). A study of 209 women aged 14–22 years reported that >99% could correctly perform and interpret a vaginal self-test by using the Osom assay, with a high correlation with clinician interpretation (96% agreement;  $\kappa = 0.87$ ) (1094). The Osom test should not be used with men because of low sensitivity (38% compared with Aptima) (1095). The Solana trichomonas assay (Quidel) is another rapid test for the qualitative detection of *T. vaginalis* DNA and can yield results <40 minutes after

specimen collection. This assay is FDA cleared for diagnosing *T. vaginalis* from female vaginal and urine specimens from asymptomatic and symptomatic women with sensitivity >98%, compared with NAAT for vaginal specimens, and >92% for urine specimens (1096). The Amplivue trichomonas assay (Quidel) is another rapid test providing qualitative detection of *T. vaginalis* that has been FDA cleared for vaginal specimens from symptomatic and asymptomatic women, with sensitivity of 90.7% and specificity of 98.9%, compared with NAAT (1097). Neither the Osom assay nor the Affirm VP III test is FDA cleared for use with specimens from men.

Culture, such as the InPouch system (BioMed Diagnostics), was considered the most sensitive method for diagnosing *T. vaginalis* infection before molecular detection methods became available. Culture has sensitivity of 44%–75% and specificity of <100% (698,1086,1098). For women, vaginal secretions are the preferred specimen type for culture because urine culture is less sensitive (698,1099,1100). For men, culture specimens require a urethral swab, urine sediment, or semen. To improve diagnostic yield, multiple specimens from men can be used to inoculate a single culture. Cultures require an incubator and are necessary for *T. vaginalis* drug susceptibility testing. The InPouch specimen should be examined daily for 5 days over a 7-day period to reduce the possibility of false negatives (1101).

Although *T. vaginalis* might be an incidental finding on a Pap test, neither conventional nor liquid-based Pap smears are considered diagnostic tests for trichomoniasis; however, women with *T. vaginalis* identified on a Pap smear should be retested with sensitive diagnostic tests and treated if infection is confirmed (1102,1103).

## Treatment

Treatment reduces symptoms and signs of *T. vaginalis* infection and might reduce transmission. Treatment recommendations for women are based on a meta-analysis (1104) and a multicenter, randomized trial of mostly symptomatic women without HIV infection (1105). The study demonstrated that multidose metronidazole (500 mg orally 2 times/day for 7 days) reduced the proportion of women retesting positive at a 1-month test of cure visit by half, compared with women who received the 2-g single dose. No published randomized trials are available that compare these doses among men.

### Recommended Regimen for Trichomoniasis Among Women

**Metronidazole** 500 mg orally 2 times/day for 7 days

### Recommended Regimen for Trichomoniasis Among Men

**Metronidazole** 2 g orally in a single dose

### Alternative Regimen for Women and Men

**Tinidazole** 2 g orally in a single dose

The nitroimidazoles are the only class of medications with clinically demonstrated efficacy against *T. vaginalis* infections. Tinidazole is usually more expensive, reaches higher levels in serum and the genitourinary tract, has a longer half-life than metronidazole (12.5 hours versus 7.3 hours), and has fewer gastrointestinal side effects (1106,1107). In randomized clinical trials, recommended metronidazole regimens have resulted in cure rates of approximately 84%–98% (1108), and the recommended tinidazole regimen has resulted in cure rates of approximately 92%–100% (1108–1112). Randomized controlled trials comparing single 2-g doses of metronidazole and tinidazole indicated that tinidazole is equivalent or superior to metronidazole in achieving parasitologic cure and symptom resolution (1110,1113,1114).

Metronidazole gel does not reach therapeutic levels in the urethra and perivaginal glands. Because it is less efficacious than oral metronidazole, it is not recommended.

## Other Management Considerations

Providers should advise persons with *T. vaginalis* infections to abstain from sex until they and their sex partners are treated (i.e., when therapy has been completed and any symptoms have resolved). Testing for other STIs, including HIV, syphilis, gonorrhea, and chlamydia, should be performed for persons with *T. vaginalis*.

## Follow-Up

Because of the high rate of reinfection among women treated for trichomoniasis, retesting for *T. vaginalis* is recommended for all sexually active women <3 months after initial treatment regardless of whether they believe their sex partners were treated (137,1115). If retesting at 3 months is not possible, clinicians should retest whenever persons next seek medical care <12 months after initial treatment. Data are insufficient to support retesting men after treatment.

## Management of Sex Partners

Concurrent treatment of all sex partners is vital for preventing reinfections. Current partners should be referred for presumptive therapy. Partners also should be advised to abstain from intercourse until they and their sex partners have been treated and any symptoms have resolved. EPT might have a role in partner management for trichomoniasis (129,1116) and can be used in states where permissible by law (<https://www.cdc.gov/std/ept/legal/default.htm>); however, no partner management intervention has been demonstrated to be superior in reducing reinfection rates (129,130). Although

no definitive data exist to guide treatment for partners of persons with persistent or recurrent trichomoniasis among whom nonadherence and reinfection are unlikely, partners might benefit from being evaluated and receiving treatment (see Recurrent Trichomoniasis).

## Recurrent Trichomoniasis

A recurrent infection can result from treatment failure (antimicrobial-resistant *T. vaginalis* or host-related problems), lack of adherence, or reinfection from an untreated sex partner. In the case of a recurrent infection, the origin of the repeat infection should be assessed because most recurrent infections likely result from reinfection. Retesting can be considered in cases of persistent or recurrent trichomoniasis with culture, the preferred test. If NAAT is used, it should not be conducted before 3 weeks after treatment completion because of possible detection of residual nucleic acid that is not clinically relevant (1117).

The nitroimidazoles are the only class of antimicrobials known to be effective against trichomonas infection. Metronidazole resistance occurs in 4%–10% of cases of vaginal trichomoniasis (1116,1118). Tinidazole resistance is less well studied but was present in 1% of infections in one study (1116). Overall, more *T. vaginalis* isolates have reported susceptibility to tinidazole than metronidazole (1119). Multidose oral metronidazole is more effective than single-dose treatment, particularly for women who are symptomatic or have a history of *T. vaginalis* (1120).

Nitroimidazole-resistant trichomoniasis is concerning because few alternatives to standard therapy exist. If treatment failure occurs in a woman after completing a regimen of metronidazole 500 mg 2 times/day for 7 days and she has been reexposed to an untreated partner, a repeat course of the same regimen is recommended. If no reexposure has occurred, she should be treated with metronidazole or tinidazole 2 g once daily for 7 days. If a man has persistent *T. vaginalis* after a single 2-g dose of metronidazole and has been reexposed to an untreated partner, he should be retreated with a single 2-g dose of metronidazole. If he has not been reexposed, he should be administered a course of metronidazole 500 mg 2 times/day for 7 days.

For persons who are experiencing persistent infection not attributable to reexposure, clinicians should request a kit from CDC to perform drug-resistance testing (<https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10239>). CDC is experienced with susceptibility testing for nitroimidazole-resistant *T. vaginalis* and can provide guidance regarding treatment in cases of drug resistance. On the basis of drug resistance testing, an alternative treatment regimen might be recommended. Treatments for infections demonstrating in vitro resistance

can include metronidazole or tinidazole 2 g daily for 7 days. If a patient has treatment failure after the 7-day regimen of high-dose oral metronidazole or tinidazole, two additional treatment options have been determined to have successful results for women. The first is high-dose oral tinidazole 2 g daily plus intravaginal tinidazole 500 mg 2 times/day for 14 days (1121). If this regimen fails, high-dose oral tinidazole (1 g 3 times/day) plus intravaginal paromomycin (4 g of 6.25% intravaginal paromomycin cream nightly) for 14 days should be considered (1122).

Alternative regimens might be effective but have not been systemically evaluated; therefore, consultation with an infectious disease specialist is recommended. Clinical improvement has been reported with intravaginal boric acid (1123,1124) but not with nitazoxanide (1123–1125). The following topically applied agents have minimal success (<50%) and are not recommended: intravaginal betadine (povidone-iodine), clotrimazole, acetic acid, furazolidone, GV, nonoxynol-9, and potassium permanganate (1126). No other topical microbicide has been reported to be effective against trichomoniasis.

## Special Considerations

### Drug Allergy, Intolerance, and Adverse Reactions

Metronidazole and tinidazole are both nitroimidazoles. Patients with an IgE-mediated-type hypersensitivity reaction to 5-nitroimidazole antimicrobials should be managed by metronidazole desensitization according to published regimens (1127,1128) and in consultation with an allergy specialist. The optimal treatment for patients with *T. vaginalis* who are unable to be desensitized has not been systematically investigated and is based on case reports, some of which report using paromomycin or boric acid for treating *T. vaginalis* (1123,1129).

### Pregnancy

*T. vaginalis* infection among pregnant women is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and delivery of infants who are small for gestational age (1075). One randomized trial of pregnant women with asymptomatic trichomoniasis reported no substantial difference in preterm birth after treatment with 2 g of metronidazole 48 hours apart during 16–23 and 24–29 weeks' gestation, compared with placebo (1130). However, that trial had multiple limitations, including use of an atypical metronidazole regimen. Another multicenter observational study of asymptomatic pregnant women in sub-Saharan African, the majority with HIV infection, reported neither trichomoniasis nor its treatment appeared to influence the risk for preterm birth or a low-birthweight infant (1131).

Although metronidazole crosses the placenta, data indicate that it poses a low risk to the developing fetus (1040,1042,1132). No evidence of teratogenicity or mutagenic effects among infants has been found in multiple cross-sectional and cohort studies among pregnant women examining single-dose (2 g) and multidose metronidazole regimens (1040,1131–1135).

Symptomatic pregnant women, regardless of pregnancy stage, should be tested and treated. Treatment of *T. vaginalis* infection can relieve symptoms of vaginal discharge for pregnant women and reduce sexual transmission to partners. Although perinatal transmission of trichomoniasis is uncommon, treatment might also prevent respiratory or genital infection in the newborn (1136,1137). Clinicians should counsel symptomatic pregnant women with trichomoniasis about the potential risks and benefits of treatment and about the importance of partner treatment and condom use in the prevention of sexual transmission. The benefit of routine screening for *T. vaginalis* in asymptomatic pregnant women has not been established.

Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are lower than those used to treat infections among infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable but remain less than maternal plasma levels (<https://www.ncbi.nlm.nih.gov/books/NBK501922>). Although multiple reported case series studies demonstrated no evidence of adverse effects among infants exposed to metronidazole in breast milk, clinicians sometimes advise deferring breastfeeding for 12–24 hours after maternal treatment with metronidazole (1051). In one study, maternal treatment with metronidazole (400 mg 3 times/day for 7 days) produced a lower concentration in breast milk and was considered compatible with breastfeeding over longer periods (1052).

Data from studies involving human subjects are limited regarding tinidazole use during pregnancy; however, animal data indicate this drug poses moderate risk. Thus, tinidazole should be avoided for pregnant women, and breastfeeding should be deferred for 72 hours after a single 2-g oral dose of tinidazole (<https://www.ncbi.nlm.nih.gov/books/NBK501922>).

## HIV Infection

Up to 53% of women with HIV have *T. vaginalis* infection (1115,1138). *T. vaginalis* infection among these women is substantially associated with pelvic inflammatory disease (1082). Among women who are not virally suppressed, treatment of trichomoniasis is associated with decreases in genital tract HIV viral load and viral shedding (1079,1139); however, no difference might occur among women who are virally suppressed (1140). Because of the high prevalence of *T. vaginalis* among women with HIV and the potential

for adverse reproductive health, poor birth outcomes, and possibly amplified HIV transmission, routine screening and prompt treatment are recommended for all women with HIV infection; screening should occur at entry to care and then at least annually thereafter.

A randomized clinical trial involving women with HIV and *T. vaginalis* infection demonstrated that a single dose of metronidazole 2 g orally was less effective than 500 mg 2 times/day for 7 days (1105). Factors that might interfere with standard single-dose treatment for trichomoniasis among women with HIV include high rates of asymptomatic BV infection, ART use, changes in vaginal ecology, and impaired immunity (1141). Thus, to improve cure rates, women with HIV who receive a diagnosis of *T. vaginalis* infection should be treated with metronidazole 500 mg orally 2 times/day for 7 days. For pregnant women with HIV, screening at the first prenatal visit and prompt treatment, as needed, are recommended because *T. vaginalis* infection is a risk factor for vertical transmission of HIV (1142).

## Treatment

Treatment reduces symptoms and signs of *T. vaginalis* infection, cures infection, and might reduce transmission. Likelihood of adverse outcomes among women with HIV infection is also reduced with *T. vaginalis* therapy.

### Recommended Regimen for Trichomonas and HIV Infection Among Women

Metronidazole 500 mg orally 2 times/day for 7 days

If a woman with HIV infection experiences treatment failure, the protocol outlined is recommended (see Recurrent Trichomonas). Other management considerations, follow-up, and management of sex partners should be performed as for women without HIV infection. Treatment of men with HIV infection should follow the same guidelines as for men without HIV.

For women with HIV who receive a diagnosis of *T. vaginalis* infection, retesting is recommended 3 months after treatment; NAAT is encouraged because of higher sensitivity of these tests. Data are insufficient to support retesting of men with trichomonas and HIV infection.

## Vulvovaginal Candidiasis

VVC usually is caused by *Candida albicans* but can occasionally be caused by other *Candida* species or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge. None of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40%–45% will have two or more episodes. On the basis of

clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated (Box 4). Approximately 10%–20% of women will have complicated VVC, requiring special diagnostic and therapeutic considerations.

## Uncomplicated Vulvovaginal Candidiasis

### Diagnostic Considerations

A diagnosis of *Candida* vaginitis is clinically indicated by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, and thick curdy vaginal discharge. Most healthy women with uncomplicated VVC have no identifiable precipitating factors. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either a wet preparation (saline, 10% KOH) of vaginal discharge demonstrates budding yeasts, hyphae, or pseudohyphae, or a culture or other test yields a positive result for a yeast species. *Candida* vaginitis is associated with normal vaginal pH (<4.5). Use of 10% KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Examination of a wet mount with KOH preparation should be performed for all women with

symptoms or signs of VVC, and women with a positive result should be treated. For those with negative wet mounts but existing signs or symptoms, vaginal cultures for *Candida* should be considered. If *Candida* cultures cannot be performed for these women, empiric treatment can be considered. Identifying *Candida* by culture in the absence of symptoms or signs is not an indication for treatment because approximately 10%–20% of women harbor *Candida* species and other yeasts in the vagina. The majority of PCR tests for yeast are not FDA cleared, and providers who use these tests should be familiar with the performance characteristics of the specific test used. Yeast culture, which can identify a broad group of pathogenic yeasts, remains the reference standard for diagnosis.

### Treatment

Short-course topical formulations (i.e., single dose and regimens of 1–3 days) effectively treat uncomplicated VVC. Treatment with azoles results in relief of symptoms and negative cultures in 80%–90% of patients who complete therapy.

#### Recommended Regimens for Vulvovaginal Candidiasis

##### Over-the-Counter Intravaginal Agents

**Clotrimazole 1% cream** 5 g intravaginally daily for 7–14 days

*or*

**Clotrimazole 2% cream** 5 g intravaginally daily for 3 days

*or*

**Miconazole 2% cream** 5 g intravaginally daily for 7 days

*or*

**Miconazole 4% cream** 5 g intravaginally daily for 3 days

*or*

**Miconazole 100 mg vaginal suppository** one suppository daily for 7 days

*or*

**Miconazole 200 mg vaginal suppository** one suppository for 3 days

*or*

**Miconazole 1,200 mg vaginal suppository** one suppository for 1 day

*or*

**Tioconazole 6.5% ointment** 5 g intravaginally in a single application

##### Prescription Intravaginal Agents

**Butoconazole 2% cream** (single-dose bioadhesive product) 5 g intravaginally in a single application

*or*

**Tercconazole 0.4% cream** 5 g intravaginally daily for 7 days

*or*

**Terconazole 0.8% cream** 5 g intravaginally daily for 3 days

*or*

**Terconazole 80 mg vaginal suppository** one suppository daily for 3 days

##### Oral Agent

**Fluconazole 150 mg orally** in a single dose

#### BOX 4. Classification of vulvovaginal candidiasis

##### Uncomplicated vulvovaginal candidiasis (VVC)

- Sporadic or infrequent VVC  
*and*
- Mild-to-moderate VVC  
*and*
- Likely to be *Candida albicans*  
*and*
- Nonimmunocompromised women

##### Complicated VVC

- Recurrent VVC (three or more episodes of symptomatic VVC in <1 year)  
*or*
- Severe VVC  
*or*
- Non-*albicans* candidiasis  
*or*
- Women with diabetes, immunocompromising conditions (e.g., HIV infection), underlying immunodeficiency, or immunosuppressive therapy (e.g., corticosteroids)

**Source:** Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. Am J Obstet Gynecol 1998;178:203–11.

The creams and suppositories in these regimens are oil based and might weaken latex condoms and diaphragms. Patients should refer to condom product labeling for further information. Even women who have previously received a diagnosis of VVC by a clinician are not necessarily more likely to be able to diagnose themselves; therefore, any woman whose symptoms persist after using an over-the-counter preparation or who has a recurrence of symptoms <2 months

after treatment for VVC should be evaluated clinically and tested. Unnecessary or unapproved use of over-the-counter preparations is common and can lead to a delay in treatment of other vulvovaginitis etiologies, which can result in adverse outcomes. No substantial evidence exists to support using probiotics or homeopathic medications for treating VVC.

## Follow-Up

Follow-up typically is not required. However, women with persistent or recurrent symptoms after treatment should be instructed to return for follow-up visits.

## Management of Sex Partners

Uncomplicated VVC is not usually acquired through sexual intercourse, and data do not support treatment of sex partners. A minority of male sex partners have balanitis, characterized by erythematous areas on the glans of the penis in conjunction with pruritus or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms.

## Special Considerations

### Drug Allergy, Intolerance, and Adverse Reactions

Topical agents usually cause no systemic side effects, although local burning or irritation might occur. Oral azoles occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has rarely been associated with abnormal elevations of liver enzymes. Clinically important interactions can occur when oral azoles are administered with other drugs (1141).

## Complicated Vulvovaginal Candidiasis

### Diagnostic Considerations

Vaginal culture or PCR should be obtained from women with complicated VVC to confirm clinical diagnosis and identify non-*albicans* *Candida*. *Candida glabrata* does not form pseudohyphae or hyphae and is not easily recognized on microscopy. *C. albicans* azole resistance is becoming more common in vaginal isolates (1144,1145), and non-*albicans* *Candida* is intrinsically resistant to azoles; therefore, culture and susceptibility testing should be considered for patients who remain symptomatic.

### Recurrent Vulvovaginal Candidiasis

Recurrent VVC, usually defined as three or more episodes of symptomatic VVC in <1 year, affects <5% of women but carries a substantial economic burden (1146). Recurrent VVC can be either idiopathic or secondary (related to frequent antibiotic use, diabetes, or other underlying host factors). The pathogenesis of recurrent VVC is poorly understood, and the majority of women with recurrent VVC have no apparent

predisposing or underlying conditions. *C. glabrata* and other non-*albicans* *Candida* species are observed in 10%–20% of women with recurrent VVC. Conventional antimycotic therapies are not as effective against these non-*albicans* yeasts as against *C. albicans*.

## Treatment

Most episodes of recurrent VVC caused by *C. albicans* respond well to short-duration oral or topical azole therapy. However, to maintain clinical and mycologic control, a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 100-mg, 150-mg, or 200-mg oral dose of fluconazole every third day for a total of 3 doses [days 1, 4, and 7]) is recommended, to attempt mycologic remission, before initiating a maintenance antifungal regimen.

Oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the indicated maintenance regimen. If this regimen is not feasible, topical treatments used intermittently can also be considered. Suppressive maintenance therapies are effective at controlling recurrent VVC but are rarely curative long-term (1147). Because *C. albicans* azole resistance is becoming more common, susceptibility tests, if available, should be obtained among symptomatic patients who remain culture positive despite maintenance therapy. These women should be managed in consultation with a specialist.

## Severe Vulvovaginal Candidiasis

Severe VVC (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) is associated with lower clinical response rates among patients treated with short courses of topical or oral therapy. Either 7–14 days of topical azole or 150 mg of fluconazole in two sequential oral doses (second dose 72 hours after initial dose) is recommended.

## Non-*albicans* Vulvovaginal Candidiasis

Because approximately 50% of women with a positive culture for non-*albicans* *Candida* might be minimally symptomatic or have no symptoms, and because successful treatment is often difficult, clinicians should make every effort to exclude other causes of vaginal symptoms for women with non-*albicans* yeast (1148). The optimal treatment of non-*albicans* VVC remains unknown; however, a longer duration of therapy (7–14 days) with a nonfluconazole azole regimen (oral or topical) is recommended. If recurrence occurs, 600 mg of boric acid in a gelatin capsule administered vaginally once daily for 3 weeks is indicated. This regimen has clinical and mycologic eradication rates of approximately 70% (1149). If symptoms recur, referral to a specialist is advised.

## Management of Sex Partners

No data exist to support treating sex partners of patients with complicated VVC. Therefore, no recommendation can be made.

## Special Considerations

### Compromised Host

Women with underlying immunodeficiency, those with poorly controlled diabetes or other immunocompromising conditions (e.g., HIV), and those receiving immunosuppression therapy (e.g., corticosteroid treatment) might not respond as well to short-term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., 7–14 days) conventional treatment is necessary.

### Pregnancy

VVC occurs frequently during pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women. Epidemiologic studies indicate a single 150-mg dose of fluconazole might be associated with spontaneous abortion (1150) and congenital anomalies; therefore, it should not be used (1151).

### HIV Infection

Vaginal *Candida* colonization rates among women with HIV infection are higher than among women without HIV with similar demographic and risk behavior characteristics, and the colonization rates correlate with increasing severity of immunosuppression (1152). Symptomatic VVC is also more frequent among women with HIV infection and similarly correlates with severity of immunodeficiency (1153). In addition, among women with HIV, systemic azole exposure is associated with isolation of non-*albicans Candida* species from the vagina.

Treatment for uncomplicated and complicated VVC among women with HIV infection should not differ from that for women who do not have HIV. Although long-term prophylactic therapy with fluconazole 200 mg weekly has been effective in reducing *C. albicans* colonization and symptomatic VVC (1154), this regimen is not recommended for women with HIV infection in the absence of complicated VVC (98). Although VVC is associated with increased HIV seroconversion among HIV-negative women and increased HIV cervicovaginal levels among women with HIV infection, the effect of treatment for VVC on HIV acquisition and transmission remains unknown.

## Pelvic Inflammatory Disease

PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis (1155–1157). Sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, often are implicated. Recent studies report that the proportion of PID cases attributable to *N. gonorrhoeae* or *C. trachomatis* is decreasing; of women who received a diagnosis of acute PID, approximately 50% have a positive test for either of those organisms (1158–1160). Micro-organisms that comprise the vaginal flora, such as strict and facultative anaerobes (1160) and *G. vaginalis*, *H. influenzae*, enteric gram-negative rods, and *Streptococcus agalactiae*, have been associated with PID (1161). In addition, cytomegalovirus (CMV), *T. vaginalis*, *M. hominis*, and *U. urealyticum* might be associated with certain PID cases (1072). Data also indicate that *M. genitalium* might have a role in PID pathogenesis (765,928) and might be associated with milder symptoms (919,923,928), although one study failed to demonstrate a substantial increase in PID after detection of *M. genitalium* in the lower genital tract (925).

Screening and treating sexually active women for chlamydia and gonorrhea reduces their risk for PID (1162,1163). Although BV is associated with PID, whether PID incidence can be reduced by identifying and treating women with BV is unclear (1161). Whether screening young women for *M. genitalium* is associated with a reduction in PID is unknown.

## Diagnostic Considerations

Acute PID is difficult to diagnose because of the considerable variation in symptoms and signs associated with this condition. Women with PID often have subtle or nonspecific symptoms or are asymptomatic. Delay in diagnosis and treatment probably contributes to inflammatory sequelae in the upper genital tract. Laparoscopy can be used to obtain a more accurate diagnosis of salpingitis and a more complete bacteriologic diagnosis. However, this diagnostic tool frequently is not readily available, and its use is not easily justifiable when symptoms are mild or vague. Moreover, laparoscopy will not detect endometritis and might not detect subtle inflammation of the fallopian tubes. Consequently, a PID diagnosis usually is based on imprecise clinical findings (1164–1166).

Data indicate that a clinical diagnosis of symptomatic PID has a positive predictive value for salpingitis of 65%–90%, compared with laparoscopy (1167–1170). The positive predictive value of a clinical diagnosis of acute PID depends on the epidemiologic characteristics of the population, with higher positive predictive values among sexually active young women (particularly adolescents), women attending STD clinics, and

those who live in communities with high rates of gonorrhea or chlamydia. Regardless of positive predictive value, no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Combinations of diagnostic findings that improve either sensitivity (i.e., detect more women who have PID) or specificity (i.e., exclude more women who do not have PID) do so only at the expense of the other. For example, requiring two or more findings excludes more women who do not have PID and reduces the number of women with PID who are identified.

Episodes of PID often go unrecognized. Although certain cases are asymptomatic, others are not diagnosed because the patient or the health care provider do not recognize the implications of mild or nonspecific symptoms or signs (e.g., abnormal bleeding, dyspareunia, and vaginal discharge). Even women with mild or asymptomatic PID might be at risk for infertility (1157). Because of the difficulty of diagnosis and the potential for damage to the reproductive health of women, health care providers should maintain a low threshold for the clinical diagnosis of PID (1158). The recommendations for diagnosing PID are intended to assist health care providers to recognize when PID should be suspected and when additional information should be obtained to increase diagnostic certainty. Diagnosis and management of other causes of lower abdominal pain (e.g., ectopic pregnancy, acute appendicitis, ovarian cyst, ovarian torsion, or functional pain) are unlikely to be impaired by initiating antimicrobial therapy for PID. Presumptive treatment for PID should be initiated for sexually active young women and other women at risk for STIs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, or if one or more of the following three minimum clinical criteria are present on pelvic examination: cervical motion tenderness, uterine tenderness, or adnexal tenderness.

More specific criteria for diagnosing PID include endometrial biopsy with histopathologic evidence of endometritis; transvaginal sonography or magnetic resonance imaging techniques demonstrating thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies indicating pelvic infection (e.g., tubal hyperemia); and laparoscopic findings consistent with PID. A diagnostic evaluation that includes some of these more extensive procedures might be warranted in certain cases. Endometrial biopsy is warranted for women undergoing laparoscopy who do not have visual evidence of salpingitis because endometritis is the only sign of PID for certain women.

Requiring that all three minimum criteria be present before the initiation of empiric treatment can result in insufficient sensitivity for a PID diagnosis. After deciding whether to initiate empiric treatment, clinicians should also

consider the risk profile for STIs. More elaborate diagnostic evaluation frequently is needed because incorrect diagnosis and management of PID might cause unnecessary morbidity. For example, the presence of signs of lower genital tract inflammation (predominance of leukocytes in vaginal secretions, cervical discharge, or cervical friability), in addition to one of the three minimum criteria, increases the specificity of the diagnosis. One or more of the following additional criteria can be used to enhance the specificity of the minimum clinical criteria and support a PID diagnosis:

- Oral temperature  $>38.3^{\circ}\text{C}$  ( $>101^{\circ}\text{F}$ )
- Abnormal cervical mucopurulent discharge or cervical friability
- Presence of abundant numbers of WBCs on saline microscopy of vaginal fluid
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

The majority of women with PID have either mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of a saline preparation of vaginal fluid (i.e., wet prep). If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, a PID diagnosis is unlikely, and alternative causes of pain should be considered. A wet prep of vaginal fluid also can detect the presence of concomitant infections (e.g., BV or trichomoniasis).

## Treatment

PID treatment regimens should provide empiric, broad-spectrum coverage of likely pathogens. Multiple parenteral and oral antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up (1171–1173). However, only a limited number of studies have assessed and compared these regimens with regard to infection elimination in the endometrium and fallopian tubes or determined the incidence of long-term complications (e.g., tubal infertility and ectopic pregnancy) after antimicrobial regimens (1159,1164,1174). The optimal treatment regimen and long-term outcome of early treatment of women with subclinical PID are unknown. All regimens used to treat PID should also be effective against *N. gonorrhoeae* and *C. trachomatis* because negative endocervical screening for these organisms does not rule out upper genital tract infection. Anaerobic bacteria have been isolated from the upper genital tract of women who have PID, and data from in vitro studies have revealed that some anaerobes (e.g., *Bacteroides fragilis*) can cause tubal and epithelial destruction. BV is often present among women who have PID (22,1160,1161,1175).

Addition of metronidazole to IM or oral PID regimens more effectively eradicates anaerobic organisms from the upper genital tract (1160). Until treatment regimens that do not cover anaerobic microbes have been demonstrated to prevent long-term sequelae (e.g., infertility and ectopic pregnancy) as successfully as the regimens that are effective against these microbes, using regimens with anaerobic activity should be considered. Treatment should be initiated as soon as the presumptive diagnosis has been made because prevention of long-term sequelae is dependent on early administration of recommended antimicrobials. For women with PID of mild or moderate clinical severity, parenteral and oral regimens appear to have similar efficacy. The decision of whether hospitalization is necessary should be based on provider judgment and whether the woman meets any of the following criteria:

- Surgical emergencies (e.g., appendicitis) cannot be excluded
- Tubo-ovarian abscess
- Pregnancy
- Severe illness, nausea and vomiting, or oral temperature >38.5°C (101°F)
- Unable to follow or tolerate an outpatient oral regimen
- No clinical response to oral antimicrobial therapy

No evidence is available to indicate that adolescents have improved outcomes from hospitalization for treatment of PID, and the clinical response to outpatient treatment is similar among younger and older women. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women.

## Parenteral Treatment

Randomized trials have demonstrated the efficacy of parenteral regimens (1160,1171,1172,1176). Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24–48 hours of clinical improvement. For women with tubo-ovarian abscesses, >24 hours of inpatient observation is recommended.

### Recommended Parenteral Regimens for Pelvic Inflammatory Disease

- |   |
|---|
| <b>Ceftriaxone</b> 1 g IV every 24 hours<br>plus              |
| <b>Doxycycline</b> 100 mg orally or IV every 12 hours<br>plus |
| <b>Metronidazole</b> 500 mg orally or IV every 12 hours<br>or |
| <b>Cefotetan</b> 2 g IV every 12 hours<br>plus                |
| <b>Doxycycline</b> 100 mg orally or IV every 12 hours<br>or   |
| <b>Cefoxitin</b> 2 g IV every 6 hours<br>plus                 |
| <b>Doxycycline</b> 100 mg orally or IV every 12 hours         |

Because of the pain associated with IV infusion, doxycycline should be administered orally when possible. Oral and IV administration of doxycycline and metronidazole provide similar bioavailability. Oral metronidazole is well absorbed and can be considered instead of IV for women without severe illness or tubo-ovarian abscess when possible. After clinical improvement with parenteral therapy, transition to oral therapy with doxycycline 100 mg 2 times/day and metronidazole 500 mg 2 times/day is recommended to complete 14 days of antimicrobial therapy.

## Alternative Parenteral Regimens

Only limited data are available to support using other parenteral second- or third- generation cephalosporins (e.g., ceftizoxime or cefotaxime). Because these cephalosporins are less active than cefotetan or cefoxitin against anaerobic bacteria, the addition of metronidazole should be considered.

Ampicillin-sulbactam plus doxycycline has been investigated in at least one clinical trial and has broad-spectrum coverage (1177). Ampicillin-sulbactam plus doxycycline is effective against *C. trachomatis*, *N. gonorrhoeae*, and anaerobes for women with tubo-ovarian abscess. Another trial demonstrated short-term clinical cure rates with azithromycin monotherapy or combined with metronidazole (1178).

When using the clindamycin and gentamicin alternative parenteral regimen, women with clinical improvement after 24–28 hours can be transitioned to clindamycin (450 mg orally 4 times/day) or doxycycline (100 mg orally 2 times/day) to complete the 14-day therapy. However, when tubo-ovarian abscess is present, clindamycin (450 mg orally 4 times/day) or metronidazole (500 mg orally 2 times/day) should be used to complete 14 days of therapy with oral doxycycline to provide more effective anaerobic coverage.

### Alternative Parenteral Regimens

- 
- |   |
|---|
| <b>Ampicillin-sulbactam</b> 3 g IV every 6 hours<br>plus  |
| <b>Doxycycline</b> 100 mg orally or IV every 12 hours<br>or   |
| <b>Clindamycin</b> 900 mg IV every 8 hours<br>plus  |
| <b>Gentamicin</b> loading dose IV or IM (2 mg/kg body weight), followed by a maintenance dose (1.5 mg/kg body weight) every 8 hours; single daily dosing (3–5 mg/kg body weight) can be substituted |

## Intramuscular or Oral Treatment

IM or oral therapy can be considered for women with mild-to-moderate acute PID because the clinical outcomes among women treated with these regimens are similar to those treated with IV therapy (1158). Women who do not respond to IM or

oral therapy within 72 hours should be reevaluated to confirm the diagnosis and be administered therapy IV.

#### Recommended Intramuscular or Oral Regimens for Pelvic Inflammatory Disease

**Ceftriaxone** 500 mg\* IM in a single dose  
 plus  
**Doxycycline** 100 mg orally 2 times/day for 14 days with **metronidazole** 500 mg orally 2 times/day for 14 days  
 or  
**Cefoxitin** 2 g IM in a single dose and **probenecid** 1 g orally administered concurrently in a single dose  
 plus  
**Doxycycline** 100 mg orally 2 times/day for 14 days with **metronidazole** 500 mg orally 2 times/day for 14 days  
 or  
**Other parenteral third-generation cephalosporin** (e.g., ceftizoxime or cefotaxime)  
 plus  
**Doxycycline** 100 mg orally 2 times/day for 14 days with **metronidazole** 500 mg orally 2 times/day for 14 days

\* For persons weighing  $\geq 150$  kg, 1 g of ceftriaxone should be administered.

These regimens provide coverage against frequent etiologic agents of PID; however, the optimal choice of a cephalosporin is unclear. Cefoxitin, a second-generation cephalosporin, has better anaerobic coverage than ceftriaxone, and, in combination with probenecid and doxycycline, has been effective in short-term clinical response among women with PID. Ceftriaxone has better coverage against *N. gonorrhoeae*. The addition of metronidazole to these regimens provides extended coverage against anaerobic organisms and will also effectively treat BV, which is frequently associated with PID.

#### Alternative Intramuscular or Oral Regimens

No data have been published regarding use of oral cephalosporins for treating PID. As a result of the emergence of quinolone-resistant *N. gonorrhoeae*, regimens that include a quinolone agent are not recommended for PID treatment. However, if the patient has cephalosporin allergy, the community prevalence and individual risk for gonorrhea are low, and follow-up is likely, alternative therapy can be considered. Use of either levofloxacin 500 mg orally once daily or moxifloxacin 400 mg orally once daily with metronidazole 500 mg orally 2 times/day for 14 days (1179–1181) or azithromycin 500 mg IV daily for 1–2 doses, followed by 250 mg orally daily in combination with metronidazole 500 mg 2 times/day for 12–14 days (1178), can be considered. Moxifloxacin is the preferred quinolone antimicrobial for *M. genitalium* infections; however, the importance of providing coverage for *M. genitalium* is unknown. Diagnostic tests for gonorrhea should be obtained before starting therapy, and persons should be managed as follows:

- If a culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility testing.
- If the isolate is determined to be quinolone-resistant *N. gonorrhoeae* or if antimicrobial susceptibility cannot be assessed (e.g., if only NAAT testing is available), consultation with an infectious disease specialist is recommended.

#### Other Management Considerations

To minimize disease transmission, women should be instructed to abstain from sexual intercourse until therapy is complete, symptoms have resolved, and sex partners have been treated (see Chlamydial Infections; Gonococcal Infections). All women who receive a diagnosis of PID should be tested for gonorrhea, chlamydia, HIV, and syphilis. The value of testing women with PID for *M. genitalium* is unknown (see *Mycoplasma genitalium*). All contraceptive methods can be continued during treatment.

#### Follow-Up

Women should demonstrate clinical improvement (e.g., defervescence; reduction in direct or rebound abdominal tenderness; and reduction in uterine, adnexal, and cervical motion tenderness)  $<3$  days after therapy initiation. If no clinical improvement has occurred  $<72$  hours after outpatient IM or oral therapy, then hospitalization, assessment of the antimicrobial regimen, and additional diagnostics, including consideration of diagnostic laparoscopy for alternative diagnoses, are recommended. All women who have received a diagnosis of chlamydial or gonococcal PID should be retested 3 months after treatment, regardless of whether their sex partners have been treated (753). If retesting at 3 months is not possible, these women should be retested whenever they next seek medical care  $<12$  months after treatment.

#### Management of Sex Partners

Persons who have had sexual contact with a partner with PID during the 60 days preceding symptom onset should be evaluated, tested, and presumptively treated for chlamydia and gonorrhea, regardless of the PID etiology or pathogens isolated. If the last sexual intercourse was  $>60$  days before symptom onset or diagnosis, the most recent sex partner should be treated. Sex partners of persons who have PID caused by *C. trachomatis* or *N. gonorrhoeae* frequently are asymptomatic. Arrangements should be made to link sex partners to care. If linkage is delayed or unlikely, EPT is an alternative approach to treating sex partners who have chlamydial or gonococcal infection (125,126) (see Partner Services). Partners should be instructed to abstain from sexual intercourse until they

and their sex partners have been treated (i.e., until therapy is completed and symptoms have resolved, if originally present).

## Special Considerations

### Drug Allergy, Intolerance, and Adverse Reactions

The risk for penicillin cross-reactivity is highest with first-generation cephalosporins but is negligible between the majority of second-generation (e.g., cefoxitin) and all third-generation (e.g., ceftriaxone) cephalosporins (619,631,653,656) (see Management of Persons Who Have a History of Penicillin Allergy).

### Pregnancy

Pregnant women suspected of having PID are at high risk for maternal morbidity and preterm delivery. These women should be hospitalized and treated with IV antimicrobials in consultation with an infectious disease specialist.

### HIV Infection

Differences in PID clinical manifestations among women with HIV infection and those without have not been well delineated (1182). In early observational studies, women with HIV infection and PID were more likely to require surgical intervention. More comprehensive observational and controlled studies have demonstrated that women with HIV infection and PID have similar symptoms, compared with women without HIV (1183–1185), except they are more likely to have a tubo-ovarian abscess. Women with HIV responded equally well to recommended parenteral and IM or oral antibiotic regimens as women without HIV. The microbiologic findings for women with HIV and women without HIV were similar, except women with HIV had higher rates of concomitant *M. hominis* and streptococcal infections. These data are insufficient for determining whether women with HIV infection and PID require more aggressive management (e.g., hospitalization or IV antimicrobial regimens).

### Intrauterine Devices

IUDs are one of the most effective contraceptive methods. Copper-containing and levonorgestrel-releasing IUDs are available in the United States. The risk for PID associated with IUD use is primarily confined to the first 3 weeks after insertion (1186–1188). If an IUD user receives a diagnosis of PID, the IUD does not need to be removed (59,1189). However, the woman should receive treatment according to these recommendations and should have close clinical follow-up. If no clinical improvement occurs within 48–72 hours of initiating treatment, providers should consider removing the IUD. A systematic review of evidence demonstrated that

treatment outcomes did not differ between women with PID who retained the IUD and those who had the IUD removed (1190). These studies primarily included women using copper-containing or other nonhormonal IUDs. No studies are available regarding treatment outcomes among women using levonorgestrel-releasing IUDs.

## Epididymitis

Acute epididymitis is a clinical syndrome causing pain, swelling, and inflammation of the epididymis and lasting <6 weeks (1191). Sometimes a testicle is also involved, a condition referred to as epididymo-orchitis. A high index of suspicion for spermatic cord (testicular) torsion should be maintained among men who have a sudden onset of symptoms associated with epididymitis because this condition is a surgical emergency.

Acute epididymitis can be caused by STIs (e.g., *C. trachomatis*, *N. gonorrhoeae*, or *M. genitalium*) or enteric organisms (i.e., *Escherichia coli*) (1192). Acute epididymitis caused by an STI is usually accompanied by urethritis, which is frequently asymptomatic. Acute epididymitis caused by sexually transmitted enteric organisms might also occur among men who are the insertive partner during anal sex. Nonsexually transmitted acute epididymitis caused by genitourinary pathogens typically occurs with bacteriuria secondary to bladder outlet obstruction (e.g., benign prostatic hyperplasia) (1193). Among older men, nonsexually transmitted acute epididymitis is also associated with prostate biopsy, urinary tract instrumentation or surgery, systemic disease, or immunosuppression. Uncommon infectious causes of nonsexually transmitted acute epididymitis (e.g., Fournier's gangrene) should be managed in consultation with a urologist.

Chronic epididymitis is characterized by a ≥6-week history of symptoms of discomfort or pain in the scrotum, testicle, or epididymis. Chronic infectious epididymitis is most frequently observed with conditions associated with a granulomatous reaction. *Mycobacterium tuberculosis* (TB) is the most common granulomatous disease affecting the epididymis and should be suspected, especially among men with a known history of or recent exposure to TB. The differential diagnosis of chronic noninfectious epididymitis, sometimes termed orchialgia or epididymalgia, is broad (e.g., trauma, cancer, autoimmune conditions, or idiopathic conditions). Men with this diagnosis should be referred to a urologist for clinical management (1191,1192).

## Diagnostic Considerations

Men who have acute epididymitis typically have unilateral testicular pain and tenderness, hydrocele, and palpable swelling

of the epididymis. Although inflammation and swelling usually begin in the tail of the epididymis, it can spread to the rest of the epididymis and testicle. The spermatic cord is usually tender and swollen. Spermatic cord (testicular) torsion, a surgical emergency, should be considered in all cases; however, it occurs more frequently among adolescents and men without evidence of inflammation or infection. For men with severe unilateral pain with sudden onset, those whose test results do not support a diagnosis of urethritis or urinary tract infection, or for whom diagnosis of acute epididymitis is questionable, immediate referral to a urologist for evaluation for testicular torsion is vital because testicular viability might be compromised.

Bilateral symptoms should increase suspicion of other causes of testicular pain. Radionuclide scanning of the scrotum is the most accurate method for diagnosing epididymitis but it is not routinely available. Ultrasound should be used primarily for ruling out torsion of the spermatic cord in cases of acute, unilateral, painful scrotal swelling. However, because partial spermatic cord torsion can mimic epididymitis on scrotal ultrasound, differentiation between spermatic cord torsion and epididymitis when torsion is not ruled out by ultrasound should be made on the basis of clinical evaluation. Although ultrasound can demonstrate epididymal hyperemia and swelling associated with epididymitis, it provides minimal diagnostic usefulness for men with a clinical presentation consistent with epididymitis. A negative ultrasound does not rule out epididymitis and thus does not alter clinical management. Ultrasound should be reserved for men if torsion of the spermatic cord is suspected or for those with scrotal pain who cannot receive an accurate diagnosis by history, physical examination, and objective laboratory findings.

All suspected cases of acute epididymitis should be evaluated for objective evidence of inflammation by one of the following POC tests:

- Gram, MB, or GV stain of urethral secretions demonstrating  $\geq 2$  WBCs per oil immersion field (737) (see Urethritis). These stains are preferred POC diagnostic tests for evaluating urethritis because they are highly sensitive and specific for documenting both urethral inflammation and presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC-containing intracellular gram-negative or purple diplococci on urethral Gram, MB, or GV stain, respectively.
- Positive leukocyte esterase test on first-void urine.
- Microscopic examination of sediment from a spun first-void urine demonstrating  $\geq 10$  WBCs/HPF.

All suspected cases of acute epididymitis should be tested for *C. trachomatis* and *N. gonorrhoeae* by NAAT. Urine is the preferred specimen for NAAT for men (553). Urine cultures for chlamydial and gonococcal epididymitis are insensitive and are not recommended. Urine bacterial cultures should also be performed for all men to evaluate for the presence of genitourinary organisms and to determine antibiotic susceptibility.

## Treatment

To prevent complications and transmission of STIs, presumptive therapy for all sexually active men is indicated at the time of the visit before all laboratory test results are available. Selection of presumptive therapy is based on risk for chlamydial and gonococcal infections or enteric organisms. Treatment goals for acute epididymitis are 1) microbiologic infection cure, 2) improvement of signs and symptoms, 3) prevention of transmission of chlamydia and gonorrhea to others, and 4) decreased potential for chlamydial or gonococcal epididymitis complications (e.g., infertility or chronic pain). Although the majority of men with acute epididymitis can be treated on an outpatient basis, referral to a specialist and hospitalization should be considered when severe pain or fever indicates other diagnoses (e.g., torsion, testicular infarction, abscess, or necrotizing fasciitis) or when men are unable to comply with an antimicrobial regimen. Age, history of diabetes, fever, and elevated C-reactive protein can indicate more severe disease requiring hospitalization (1193).

### Recommended Regimens for Epididymitis

**For acute epididymitis most likely caused by chlamydia or gonorrhea:**

**Ceftriaxone** 500 mg\* IM in a single dose

*plus*

**Doxycycline** 100 mg orally 2 times/day for 10 days

**For acute epididymitis most likely caused by chlamydia, gonorrhea, or enteric organisms (men who practice insertive anal sex):**

**Ceftriaxone** 500 mg\* IM in a single dose

*plus*

**Levofloxacin** 500 mg orally once daily for 10 days

**For acute epididymitis most likely caused by enteric organisms only:**  
**Levofloxacin** 500 mg orally once daily for 10 days

\* For persons weighing  $\geq 150$  kg, 1 g of ceftriaxone should be administered.

Levofloxacin monotherapy should be considered if the infection is most likely caused by enteric organisms only, and gonorrhea has been ruled out by Gram, MB, or GV stain. This includes men who have undergone prostate biopsy, vasectomy, and other urinary tract instrumentation procedures. Treatment should be guided by bacterial cultures and antimicrobial susceptibilities. As an adjunct to therapy, bed rest, scrotal elevation, and nonsteroidal anti-inflammatory drugs are

recommended until fever and local inflammation have subsided. Complete resolution of discomfort might not occur for a few weeks after completion of the antibiotic regimen.

## Other Management Considerations

Men who have acute epididymitis confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be advised to abstain from sexual intercourse until they and their partners have been treated and symptoms have resolved. All men with acute epididymitis should be tested for HIV and syphilis.

## Follow-Up

Men should be instructed to return to their health care providers if their symptoms do not improve <72 hours after treatment. Signs and symptoms of epididymitis that do not subside in <3 days require reevaluation of the diagnosis and therapy. Men who experience swelling and tenderness that persist after completion of antimicrobial therapy should be evaluated for alternative diagnoses, including tumor, abscess, infarction, testicular cancer, TB, and fungal epididymitis.

## Management of Sex Partners

Men who have acute sexually transmitted epididymitis confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer all sex partners during the previous 60 days before symptom onset for evaluation, testing, and presumptive treatment (see Chlamydial Infections; Gonococcal Infections). If the last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be evaluated and treated. Arrangements should be made to link sex partners to care. EPT is an effective strategy for treating sex partners of men who have or are suspected of having chlamydia or gonorrhea for whom linkage to care is anticipated to be delayed (125,126) (see Partner Services). Partners should be instructed to abstain from sexual intercourse until they and their sex partners are treated and symptoms have resolved.

## Special Considerations

### Drug Allergy, Intolerance, and Adverse Reactions

The risk for penicillin cross-reactivity is negligible between all third-generation cephalosporins (e.g., ceftriaxone) (658,681) (see Management of Persons Who Have a History of Penicillin Allergy). Alternative regimens have not been studied; therefore, clinicians should consult an infectious disease specialist if such regimens are required.

## HIV Infection

Men with HIV infection who have uncomplicated acute epididymitis should receive the same treatment regimen as those who do not have HIV. Other etiologic agents have been implicated in acute epididymitis among men with HIV, including CMV, salmonella, toxoplasmosis, *U. urealyticum*, *Corynebacterium* species, *Mycoplasma* species, and *Mima polymorpha* (1192).

## Human Papillomavirus Infections

Approximately 150 types of HPV have been identified, at least 40 of which infect the genital area (1194). The majority of HPV infections are self-limited and are asymptomatic or unrecognized. Sexually active persons are usually exposed to HPV during their lifetime (838,1195,1196). Oncogenic, high-risk HPV infection (e.g., HPV types 16 and 18) causes the majority of cervical, penile, vulvar, vaginal, anal, and oropharyngeal cancers and precancers (1197), whereas other HPV infection (e.g., HPV types 6 and 11) causes genital warts and recurrent respiratory papillomatosis. Persistent oncogenic HPV infection is the strongest risk factor for development of HPV-attributable precancers and cancers. A substantial proportion of cancers and anogenital warts are attributable to HPV in the United States. An estimated 34,800 new HPV-attributable cancers occurred every year during 2012–2016 (1198). Before HPV vaccines were introduced, approximately 355,000 new cases of anogenital warts occurred every year (1199).

## Prevention

### HPV Vaccines

Three HPV vaccines are licensed in the United States: Cervarix, a 2-valent vaccine (2vHPV) that targets HPV types 16 and 18; Gardasil, a 4-valent vaccine (4vHPV) that targets HPV types 6, 11, 16, and 18; and Gardasil 9, a 9-valent vaccine (9vHPV) that targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Types 16 and 18 account for 66% of all cervical cancers, whereas the five additional types targeted by the 9-valent vaccine account for 15%. Types 6 and 11 cause >90% of genital warts. Only 9vHPV vaccine is available in the United States.

ACIP recommendations for HPV vaccination (<https://www.cdc.gov/vaccines/hcp/acip-recommendations/vaccine-specific/hpv.html>) include the following:

- Routine HPV vaccination for all adolescents at age 11 or 12 years.
- Administering vaccine starting at age 9 years.

- Catch-up vaccination through age 26 years for those not vaccinated previously.
- Not using HPV vaccination for all adults aged >26 years. Instead, shared clinical decision-making between a patient and a provider regarding HPV vaccination is recommended for certain adults aged 27–45 years not vaccinated previously.
- A 2-dose vaccine schedule (at 0- and 6–12-month intervals) is recommended for persons who initiate vaccination before their 15th birthday.
- A 3-dose vaccine schedule (at 0-, 1–2-, and 6-month intervals) for immunocompromised persons regardless of age of initiation.

HPV vaccines are not recommended for use in pregnant women. HPV vaccines can be administered regardless of history of anogenital warts, abnormal Pap test or HPV test, or anogenital precancer. Women who have received HPV vaccine should continue routine cervical cancer screening (see Cervical Cancer). HPV vaccine is available for eligible children and adolescents aged <19 years through the Vaccines for Children (VFC) program (additional information is available at <https://www.cdc.gov/vaccines/programs/vfc/index.html> or by calling CDC INFO 800-232-4636). For uninsured persons aged <19 years, patient assistance programs are available from the vaccine manufacturers. Prelicensure and postlicensure safety evaluations have determined that the vaccine is well tolerated. With >120 million doses of HPV vaccines distributed in the United States, robust data demonstrate that HPV vaccines are safe (<https://www.cdc.gov/vaccinesafety>). Impact-monitoring studies in the United States have demonstrated reductions of genital warts as well as the HPV types contained within the quadrivalent vaccine (1200–1203). Settings that provide STI services should either administer the vaccine to eligible clients within the routine and catch-up age groups through age 26 years who have not started or completed the vaccine series, or link these persons to another facility equipped to provide the vaccine. Clinicians providing services to children, adolescents, and young adults should be knowledgeable about HPV and the vaccine (<https://www.cdc.gov/vaccines/who/teens/for-hcp/hpv-resources.html>). HPV vaccination has not been associated with initiation of sexual activity or sexual risk behaviors (1204,1205).

Abstaining from sexual activity is the most reliable method for preventing genital HPV infection. Persons can decrease their chances of infection by practicing consistent and correct condom use and limiting their number of sex partners. Although these interventions might not fully protect against HPV, they can decrease the chances of HPV acquisition and transmission.

## Diagnostic Considerations

HPV tests are available for detecting oncogenic types of HPV infection and are used in the context of cervical cancer screening and management or follow-up of abnormal cervical cytology or histology (see Cervical Cancer). These tests should not be used for male partners of women with HPV or women aged <25 years, for diagnosis of genital warts, or as a general STI test.

Application of 3%–5% acetic acid, which might cause affected areas to turn white, has been used by certain providers to detect genital mucosa infected with HPV. The routine use of this procedure to detect mucosal changes attributed to HPV infection is not recommended because the results do not influence clinical management.

## Treatment

Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV. Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection. Precancerous lesions are detected through cervical cancer screening; HPV-related precancer should be managed on the basis of existing guidance (see Cervical Cancer).

## Counseling

### Key Messages for Persons with Human Papillomavirus Infection

When counseling persons with anogenital HPV infection, the provider should discuss the following:

- Anogenital HPV infection is common. It usually infects the anogenital area but can infect other areas, including the mouth and throat. The majority of sexually active persons get HPV at some time during their lifetime, although most never know it.
- Partners tend to share HPV, and it is not possible to determine which partner transmitted the original infection. Having HPV does not mean that a person or his or her partner is having sex outside the relationship.
- Persons who acquire HPV usually clear the infection spontaneously, meaning that HPV becomes undetectable with no associated health problems.
- If HPV infection persists, genital warts, precancers, and cancers of the cervix, anus, penis, vulva, vagina, head, or neck might develop.
- Discussion of tobacco use, and provision of cessation counseling, is important because of its contribution to the progression of precancer and cancer.
- The types of HPV that cause genital warts are different from the types that can cause cancer.

- Many types of HPV are sexually transmitted through anogenital contact, mainly during vaginal and anal sex. HPV also might be transmitted during oral sex and genital-to-genital contact without penetration. In rare cases, a pregnant woman can transmit HPV to an infant during delivery.
- Treatments are available for the conditions caused by HPV but not for the virus itself.
- Having HPV does not make it harder for a woman to get pregnant or carry a pregnancy to term. However, certain precancers or cancers that HPV can cause, and the surgical procedures needed to treat them, can affect a woman's ability to get pregnant or carry a pregnancy to term.
- No HPV test can determine which HPV infection will become undetectable and which will persist or progress to disease. However, in certain circumstances, HPV tests can determine whether a woman is at increased risk for cervical cancer. These tests are not for detecting other HPV-related problems, nor are they useful for women aged <25 years or men of any age.

## Prevention

- Three HPV vaccines can prevent diseases and cancers caused by HPV. The 2vHPV, 4vHPV, and 9vHPV vaccines protect against the majority of cervical cancer cases, although the 4vHPV and 9vHPV vaccines also protect against the majority of genital warts. Only 9vHPV vaccine is available in the United States. HPV vaccines are safe and effective and are recommended routinely for adolescents aged 11–12 years. Catch-up vaccination is also recommended for older adolescents and young adults through age 26 years (<https://www.cdc.gov/hpv/hcp/index.html>). Shared clinical decision-making is recommended regarding HPV vaccination for certain adults aged 27–45 years who are not adequately vaccinated per guidance (<https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6832a3-H.pdf>).
- Condoms used consistently and correctly can lower the chances of acquiring and transmitting HPV and developing HPV-related diseases (e.g., genital warts or cervical cancer). However, because HPV can infect areas not covered by a condom, condoms might not fully protect against HPV.
- Limiting the number of sex partners can reduce the risk for HPV. However, even persons with only one lifetime sex partner can get HPV.
- Abstaining from sexual activity is the most reliable method for preventing genital HPV infection.

## Anogenital Warts

Anogenital warts are a common disease, and 90% are caused by nononcogenic HPV types 6 or 11. These types can be

commonly identified before or at the same time anogenital warts are detected (1206). HPV types 16, 18, 31, 33, and 35 also are occasionally identified in anogenital warts (usually as infections with HPV 6 or 11) and can be associated with foci of high-grade squamous intraepithelial lesion (HSIL), particularly among persons who have HIV infection. In addition to anogenital warts, HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts.

Anogenital warts are usually asymptomatic; however, depending on the size and anatomic location, they can be painful or pruritic. They are usually flat, papular, or pedunculated growths on the genital mucosa. Anogenital warts occur commonly at certain anatomic sites, including around the vaginal introitus, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Warts can also occur at multiple sites in the anogenital epithelium or within the anogenital tract (e.g., cervix, vagina, urethra, perineum, perianal skin, anus, or scrotum). Intra-anal warts are observed predominantly in persons who have had receptive anal intercourse; however, they also can occur among men and women who have not had a history of anal sexual contact.

## Prevention

Anogenital warts have decreased among adolescents, young women, and heterosexual men with use of HPV vaccination in multiple countries, including the United States (1203,1207–1216).

## Diagnostic Considerations

Diagnosis of anogenital warts is usually made by visual inspection but can be confirmed by biopsy, which is indicated if lesions are atypical (e.g., pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated lesions). Biopsy might also be indicated in the following circumstances, particularly if the patient is immunocompromised (including those with HIV infection): the diagnosis is uncertain, the lesions do not respond to standard therapy, or the disease worsens during therapy. HPV testing is not recommended for anogenital wart diagnosis because test results are not confirmatory and do not guide genital wart management. Some anogenital lesions can resemble anogenital warts (condyloma acuminata), but do not respond to anogenital wart treatment. Condyloma lata, a manifestation of secondary syphilis, can be diagnosed by serologic tests or through direct detection from serous fluid from the lesions (see Syphilis, Diagnostic Considerations).

## Treatment

The aim of treatment is removal of the warts and amelioration of symptoms, if present. The appearance of warts also can result in considerable psychosocial distress, and removal can relieve

cosmetic concerns. For most patients, treatment results in resolution of the warts. If left untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. Because warts might spontaneously resolve in <1 year, an acceptable alternative for certain persons is to forego treatment and wait for spontaneous resolution. Available therapies for anogenital warts might reduce, but probably do not eradicate, HPV infectivity. Whether reduction in HPV viral DNA resulting from treatment reduces future transmission remains unknown.

Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. No definitive evidence indicates that any one recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts. Shared clinical decision-making between a patient and a provider regarding treatment algorithms has been associated with improved clinical outcomes and should be encouraged. Because all available treatments have shortcomings, clinicians sometimes use combination therapy (e.g., provider-administered cryotherapy with patient-applied topical therapy between visits to the provider). However, limited data exist regarding the efficacy or risk for complications associated with combination therapy. Treatment regimens are classified as either patient-applied or provider-administered modalities. Patient-applied modalities are preferred by certain persons because they can be administered in the privacy of their home. To ensure that patient-applied modalities are effective, instructions should be provided to patients while in the clinic, and all anogenital warts should be accessible and identified during the clinic visit. Follow-up visits after weeks of therapy enable providers to answer any questions about use of the medication, address any side effects experienced, and facilitate assessment of the response to treatment.

#### **Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus)\***

**Patient-applied:** Imiquimod 3.75% or 5% cream<sup>†</sup>

or

Podofilox 0.5% solution or gel

or

Sinecatechins 15% ointment<sup>†</sup>

**Provider-administered:** Cryotherapy with liquid nitrogen or cryoprobe

or

**Surgical removal** by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery

or

Trichloroacetic acid (TCA) or bichloroacetic acid (BCA)  
80%–90% solution

\* Persons with external anal or perianal warts might also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.

<sup>†</sup> Might weaken condoms and vaginal diaphragms.

Imiquimod is a patient-applied, topically active immune enhancer that stimulates production of interferon and other cytokines. Imiquimod 5% cream should be applied once at bedtime, 3 times/week for <16 weeks (1217). Similarly, imiquimod 3.75% cream should be applied once at bedtime every night for <8 weeks (1218). With either formulation, the treatment area should be washed with soap and water 6–10 hours after the application. Local inflammatory reactions, including redness, irritation, induration, ulceration or erosion, and vesicles might occur with using imiquimod, and hypopigmentation has also been described (1219). Limited case reports demonstrate an association between treatment with imiquimod cream and worsened inflammatory or autoimmune skin diseases (e.g., psoriasis, vitiligo, or lichenoid dermatoses) (1220–1222). Data from studies of human participants are limited regarding use of imiquimod during pregnancy; however, animal data indicate that this therapy poses low risk (431).

Podofilox (podophyllotoxin) is a patient-applied antimitotic drug that causes wart necrosis. Podofilox solution (using a cotton swab) or podofilox gel (using a finger) should be applied to anogenital warts 2 times/day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm<sup>2</sup>, and the total volume of podofilox should be limited to 0.5 mL/day. If possible, the health care provider should apply the initial treatment to demonstrate proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. After each treatment, the gel or solution should be allowed to dry. Patients should wash their hands before and after each application. Podofilox is contraindicated during pregnancy (431).

Sinecatechins is a patient-applied, green-tea extract with an active product (catechins). Sinecatechins 15% ointment should be applied 3 times/day (0.5-cm strand of ointment to each wart) by using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. This product should not be continued for >16 weeks (1223–1225). The medication should not be washed off after use. Genital, anal, and oral sexual contact should be avoided while the ointment is on the skin. The most common side effects of sinecatechins are erythema, pruritus or burning, pain, ulceration, edema, induration, and vesicular rash. This medication is not recommended for persons with HIV infection, other immunocompromised conditions, or genital herpes because the safety and efficacy of therapy has not been evaluated. The safety of sinecatechins during pregnancy is unknown.

Cryotherapy is a provider-administered therapy that destroys warts by thermal-induced cytolysis. Health care providers should be trained on the correct use of this therapy because overtreatment or undertreatment can result in complications or low efficacy. Pain during and after application of the liquid

nitrogen, followed by necrosis and sometimes blistering, is common. Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large. Surgical therapy has the advantage of eliminating the majority of warts at a single visit, although recurrence can occur. Surgical removal requires substantial clinical training, additional equipment, and sometimes a longer office visit. After local anesthesia is applied, anogenital warts can be physically destroyed by electrocautery, in which case no additional hemostasis is required. Care should be taken to control the depth of electrocautery to prevent scarring. Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by CO<sub>2</sub> laser, or by curettage. Because most warts are exophytic, this procedure can be accomplished with a resulting wound that only extends into the upper dermis. Hemostasis can be achieved with an electrocautery unit or, in cases of minor bleeding, a chemical styptic (e.g., an aluminum chloride solution). Suturing is neither required nor indicated in the majority of cases. For patients with large or extensive warts, surgical therapy, including CO<sub>2</sub> laser, might be most beneficial; such therapy might also be useful for intraurethral warts, particularly for those persons whose warts have not responded to other treatments. Treatment of anogenital and oral warts should be performed in a ventilated room by using standard precautions (<https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html/Isolation2007.pdf#page>) and local exhaust ventilation (e.g., a smoke evacuator) (1226).

Trichloroacetic acid (TCA) and bichloroacetic acid (BCA) are provider-administered caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. TCA solution has a low viscosity, comparable with that of water, and can spread rapidly and damage adjacent tissues if applied excessively. A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. TCA or BCA treatment can be repeated weekly if necessary.

### Alternative Regimens for External Genital Warts

Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits

and risks of these regimens should be provided. In addition, alternative regimens might be associated with more side effects. Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours (1227–1229). Podophyllin resin 10%–25% in a compound tincture of benzoin might be considered for provider-administered treatment under conditions of strict adherence to recommendations. Podophyllin should be applied to each wart and then allowed to air dry before the treated area comes into contact with clothing. Overapplication or failure to air dry can result in local irritation caused by spread of the compound to adjacent areas and possible systemic toxicity. The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, application should be limited to <0.5 mL of podophyllin or an area of <10 cm<sup>2</sup> of warts per session; the area to which treatment is administered should not contain any open lesions, wounds, or friable tissue; and the preparation should be thoroughly washed off 1–4 hours after application. Podophyllin resin preparations differ in the concentration of active components and contaminants. Shelf life and stability of podophyllin preparations are unknown. The safety of podophyllin during pregnancy has not been established.

#### Recommended Regimens for Urethral Meatus Warts

Cryotherapy with liquid nitrogen  
or  
Surgical removal

#### Recommended Regimens for Vaginal Warts

Cryotherapy with liquid nitrogen  
The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.  
or  
Surgical removal  
or  
Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

#### Recommended Regimens for Cervical Warts

Cryotherapy with liquid nitrogen  
or  
Surgical removal  
or  
Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

Management of cervical warts should include consultation with a specialist. For women who have exophytic cervical warts, a biopsy evaluation to exclude HSIL should be performed before treatment is initiated.

**Recommended Regimens for Intra-Anal Warts**

- Cryotherapy with liquid nitrogen  
*or*
- Surgical removal**  
*or*
- Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

Management of intra-anal warts should include consultation with a colorectal specialist.

**Follow-Up**

Anogenital warts typically respond within 3 months of therapy. Factors that might affect response to therapy include immunosuppression and treatment compliance. Warts located on moist surfaces or in intertriginous areas respond best to topical treatment. A new treatment modality should be selected when no substantial improvement is observed after a complete course of treatment or in the event of severe side effects; treatment response and therapy-associated side effects should be evaluated throughout the therapy course. Complications occur rarely when treatment is administered correctly. Persistent hypopigmentation or hyperpigmentation can occur with ablative modalities (e.g., cryotherapy and electrocautery) and have been described with immune modulating therapies (e.g., imiquimod cream). Depressed or hypertrophic scars are uncommon but can occur, especially if patients have insufficient time to heal between treatments. Rarely, treatment can result in chronic pain syndromes (e.g., vulvodynia and hyperesthesia of the treatment site) or, in the case of anal warts, painful defecation or fistulas.

**Counseling**

When counseling persons with anogenital warts, the provider should discuss the following:

- If left untreated, genital warts might resolve, stay the same, or increase in size or number. The types of HPV that cause genital warts are different from the types that can cause cancer.
- Women with genital warts do not need Pap tests more often than other women.
- Time of HPV acquisition cannot be definitively determined. Genital warts can develop months or years after acquiring HPV.
- HPV types that cause genital warts can be passed on to another person, even without visible signs of warts. Sex partners tend to share HPV, even though signs of HPV (e.g., warts) might occur in only one or neither partner.
- Although genital warts are common and benign, certain persons might experience considerable psychosocial impact after receiving this diagnosis.

- Although genital warts can be treated, such treatment does not cure the virus itself. For this reason, genital warts often recur after treatment, especially during the first 3 months.
- Because genital warts can be sexually transmitted, persons with genital warts benefit from testing for other STIs. HPV might remain present and can still be transmitted to partners even after the warts are gone.
- Condoms might lower the chances of transmitting genital warts if used consistently and correctly; however, HPV can infect areas that are not covered by a condom and might not fully protect against HPV.
- A vaccine is available for males and females to prevent genital warts (Gardasil 9) but it will not treat existing HPV or genital warts. This vaccine can prevent the majority of cases of genital warts among persons who have not yet been exposed to wart-causing types of HPV.

**Management of Sex Partners**

Persons should inform current partners about having genital warts because the types of HPV that cause warts can be passed on to partners. Partners should be counseled that they might already have HPV despite no visible signs of warts; therefore, HPV testing of sex partners of persons with genital warts is not recommended. Partners might benefit from a physical examination to detect genital warts and tests for other STIs. No recommendations can be made regarding informing future sex partners about a diagnosis of genital warts because the duration of viral persistence after warts have resolved is unknown.

**Special Considerations****Pregnancy**

Podofilox, podophyllin, and sinecatechins should not be used during pregnancy. Imiquimod appears to pose low risk but should be avoided until more data are available. Anogenital warts can proliferate and become friable during pregnancy. Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete. Rarely, HPV types 6 and 11 can cause respiratory papillomatosis among infants and children, although the route of transmission (i.e., transplacental, perinatal, or postnatal) is not completely understood. Whether cesarean delivery prevents respiratory papillomatosis among infants and children also is unclear (1230); therefore, cesarean delivery should not be performed solely to prevent transmission of HPV infection to the newborn. Cesarean delivery is indicated for women with anogenital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding. Pregnant women with anogenital warts should be counseled about the low risk

for warts on the larynx of their infants or children (recurrent respiratory papillomatosis).

### HIV and Other Causes of Immunosuppression

Persons with HIV infection or who are otherwise immunosuppressed are more likely to develop anogenital warts than those who do not have HIV (1231). Moreover, such persons can have larger or more numerous lesions, might not respond to therapy as well as those who are immunocompetent, and might have more frequent recurrences after treatment (1231,1232–1234). Despite these factors, data do not support altered approaches to treatment for persons with HIV infection. Squamous cell carcinomas arising in or resembling anogenital warts might occur more frequently among immunosuppressed persons, therefore requiring biopsy for confirmation of diagnosis for suspicious cases (1235–1237).

### High-Grade Squamous Intraepithelial Lesions

Biopsy of an atypical wart might reveal HSIL or cancer of the anogenital tract. In this instance, referral to a specialist for treatment is recommended.

### Cancers and Precancers Associated with Human Papillomavirus

Persistent infection with high-risk (oncogenic) types of HPV has a causal role in approximately all cervical cancers and in certain vulvar, vaginal, penile, anal, and oropharyngeal cancers (1238). However, cervical cancer is the only HPV-associated cancer for which routine screening is recommended.

## Cervical Cancer

### Screening Recommendations

Recommendations for cervical cancer screening in the United States are based on systematic evidence reviews by major medical and advocacy organizations, including USPSTF (174), ACS (177), and ACOG (175). Over time, general alignment across these organizations has emerged as to when to start and end cervical cancer screening as well as the periodicity of screening. Although no single guideline universally guides screening practices in the United States, the Patient Protection and Affordable Care Act required Medicaid and new private health insurance plans to provide coverage for preventive services graded A or B by USPSTF, which includes cervical cancer screening. In addition, the National Center for Quality Assurance provides a set of measures (the Healthcare Effectiveness Data and Information Set [HEDIS]) for up-to-date cervical cancer screening that aligns with USPSTF recommendations (<https://www.ncqa.org/hedis/measures/cervical-cancer-screening>). The Center for Medicaid and

Medicare Services uses the same measure as HEDIS to measure cervical cancer screening performance.

USPSTF screening recommendations apply to persons with a cervix at average risk, defined as those with no previous cervical cancer or high-grade precancer, not currently under close follow-up for a recent abnormal result, not immunocompromised (e.g., persons with HIV), and who had no exposure to diethylstilbestrol in utero. Among these persons, screening should be performed starting at age 21 years and continue through age 65 years. Testing can be performed using either conventional or liquid-based cytologic tests (i.e., Pap tests). For persons aged ≥30 years, screening can include FDA-cleared tests for high-risk, oncogenic types of HPV. For cytopathologic testing, clinics should use CLIA-certified laboratories using acceptable terminology (Bethesda 2001 or LAST terminology) (1239).

Annual cervical cancer screening is not recommended for persons at average risk. Instead, cytology testing is recommended every 3 years for persons aged 21–29 years. For persons aged 30–65 years, a cytology test every 3 years, an HPV test alone every 5 years, or a cytology test plus an HPV test (cotest) every 5 years is recommended. Cotesting can be done by either collecting one sample for the cytology test and another for the HPV test or by using the remaining liquid cytology material for the HPV test. Cervical screening programs should screen those who have received HPV vaccination in the same manner as those that are unvaccinated. Screening is not recommended before age 21 years among those at average risk. For those aged 30–65 years, cytology alone or primary HPV testing is preferred by USPSTF; however, cotesting can be used as an alternative approach. ACOG (1240), ACS (177), and USPSTF (174) each have screening recommendations (1241) (Table 1).

Clinics should weigh the benefits of each screening strategy as well as their resources, such as time and cost, in deciding on which of the three possible screening strategies to implement. Decision analytic models (1242) estimating the benefits, harms, and costs (1243) of several different strategies might be useful in making this determination (174,1244,1245). Adopting recommended screening and follow-up procedures, including screening methods, results provision, and follow-up, can lead to success in implementing cervical cancer screening in clinics (1246).

Patients should be provided a copy of their test results; those with normal results should be provided information on follow-up visits and the importance of continued cervical cancer screening, if applicable. Those with abnormal screening tests should be managed per published guidelines. National consensus guidelines are available for the management of abnormal cervical cancer screening tests (1247). HPV testing or cotesting is preferred to cytology alone for surveillance after an abnormal screening test result. These guidelines base

**TABLE 1. Cervical cancer screening and surveillance recommendations**

Population	Screening specifics	Guideline group, yr of recommendation		
		USPSTF, 2018	ACOG, 2016	ACS, 2020
Persons at average risk	Age to start screening	21 yrs	21 yrs	25 yrs
	Age to end screening	65 yrs	65 yrs	65 yrs
	Screening test options and intervals	If three consecutive negative cytology tests or two negative cytology plus HPV tests or two negative HPV tests (ACS) with the most recent within the previous 5 yrs and no abnormal tests within the previous 10 yrs (ACS) and no CIN 2 or CIN 3 within the previous 25 yrs	Aged 21–65 yrs: Cytology alone every 3 yrs or Aged 21–29 yrs: Cytology alone every 3 yrs Aged 30–65 yrs: Cytology plus HPV testing every 5 yrs or Aged 21–29 yrs: Cytology alone every 3 yrs Aged 30–65: HPV testing alone every 5 yrs*	HPV testing alone every 5 yrs or Cytology plus HPV testing every 5 yrs or Cytology alone every 3 yrs
	Preferred strategies	Cytology alone every 3 yrs and HPV testing alone every 5 yrs (equally preferred)	Cytology plus HPV testing every 5 yrs	HPV testing alone every 5 yrs
	Previous hysterectomy with removal of cervix	Screening not recommended after hysterectomy for benign indications Surveillance testing recommended for previous diagnosis of high-grade precancer, AIS, or cancer		
	Age to start screening	No specific recommendation	Within 1 yr of onset of sexual activity or, if already sexually active, within the first year after HIV or other immunocompromising medical condition diagnosis but no later than age 21 yrs	
	Age to end screening Screening test options and intervals		None; lifelong screening recommended Aged 21–65 yrs: Cytology every year; after three consecutive annual normal cytology test results, screening can be every 3 yrs or Aged 21–29 yrs: Cytology every year Aged 30–65 yrs: Cytology plus HPV testing every 3 yrs	
Persons with an immunocompromising medical condition <sup>†</sup> (e.g., HIV infection or solid organ transplantation)	Previous hysterectomy with removal of cervix		Not specified	
	Age to start screening	No specific recommendation	Not specified	No specific recommendation
	Age to end screening		Not specified	
	Screening test options and intervals		Cytology alone annually	
Persons with in utero exposure to diethylstilbestrol <sup>§</sup>	Previous hysterectomy with removal of cervix		Not specified	
	Age to start screening	No specific recommendation	Not specified	
	Age to end screening		Not specified	
	Screening test options and intervals		Cytology alone annually	
Persons who have received HPV vaccination	No changes to the screening approaches above			
Population	<b>ASCCP, 2019, and ACOG, 2020</b>			
	Persons with a diagnosis of CIN 2 or CIN 3 (histologic HSIL <sup>¶</sup> ) within the previous 25 yrs	Not applicable		
	Age to start screening	May end at age 65 yrs if CIN diagnosis ≥25 yrs ago and criteria for ending screening met, otherwise continue screening past age 65 yrs		
	Age to end screening	Continued screening for ≥25 yrs after diagnosis is acceptable if patient is in good health		
	Screening test options and intervals	<b>Initial surveillance:</b> HPV testing alone or cytology plus HPV testing at 6, 18, and 30 mos or Cytology at 6, 12, 18, 24, and 30 mos		
	Previous hysterectomy with removal of cervix	<b>Long-term surveillance:</b> HPV testing alone or cytology plus HPV testing every 3 yrs or Cytology alone annually Continue for ≥25 yrs from the initial CIN diagnosis, even if extends past age 65 yrs Routine screening can resume after the posttreatment surveillance period		
		HPV testing alone or cytology plus HPV testing every 3 yrs or Cytology alone annually Continue for ≥25 yrs from the initial CIN diagnosis, even if extends past age 65 yrs		

**Source:** Perkins R, Guido R, Saraiya M, et al. Summary of current guidelines for cervical cancer screening and management of abnormal test results: 2016–2020. *J Womens Health (Larchmt)* 2021;30:5–13.

**Abbreviations:** ACS = American Cancer Society; ACOG = American College of Obstetricians and Gynecologists; AIS = adenocarcinoma in situ; ASCCP = American Society for Colposcopy and Cervical Pathology; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; USPSTF = U.S. Preventive Services Task Force.

\* Considered an alternative screening strategy by ACOG.

† Panel for Opportunistic Infections, ACOG, 2016.

‡ ACOG, 2016.

¶ Either by cytology or by histology; includes a persistent cytologic diagnosis of atypical squamous cells, cannot rule out HSIL.

management recommendations on case-by-case assessment of risk considering past screening history and current results (see Follow-Up). Patients with abnormal cervical cancer screening test results should be counseled about those results (see Counseling Messages).

The following additional management considerations are associated with performing Pap tests and HPV tests:

- Cytology (Pap tests) and HPV tests should not be considered screening tests for STIs.
- All persons with a cervix should receive cervical cancer screening, regardless of sexual orientation or gender identity (i.e., those who identify as lesbian, bisexual, heterosexual, or transgender).
- A conventional cytology test (in which the sample is smeared onto a dry slide) should ideally be scheduled for 10–20 days after the first day of menses. Liquid-based cytology can be performed at any time during the menstrual cycle.
- If specific infections other than HPV (e.g., chlamydia or gonorrhea) are identified at the visit, a repeat cytology test after appropriate treatment for those infections might be indicated. However, in most instances (even in the presence of certain severe cervical infections), cytology tests will be reported as satisfactory for evaluation, and reliable final reports can be produced without the need to repeat the cytology test after treatment.
- The presence of a mucopurulent discharge should not postpone cytology testing. The test can be performed after removal of the discharge with a saline-soaked cotton swab.
- HPV testing can be performed either as a separate test or by using material from the liquid-based cytology specimen.
- In the absence of other indications, the presence of external genital warts does not warrant more frequent cervical cancer screening.
- The sequence of cytology testing in relation to collection of other endocervical specimens does not influence Pap test results or their interpretation (600). Typically, vaginal specimens are preferred for chlamydia and gonorrhea screening; however, during a pelvic examination, endocervical specimens for STI testing can be collected first.
- Persons who have had a total hysterectomy with removal of the cervix do not require screening unless cervical intraepithelial neoplasia (CIN) 2, CIN 3, or adenocarcinoma in situ was diagnosed within the previous 20 years (175,1247). If the cervix remains intact after a supracervical hysterectomy, regularly scheduled Pap tests should be performed as indicated (1248–1250).
- Health care facilities that train providers on cytology test collection and use simple quality assurance measures are

more likely to obtain satisfactory test results (as determined by the laboratory).

- The use of instruments designed to sample the cervical transformation zone (e.g., cytobrushes) improves the accuracy of cytology tests (1251).
- Both liquid-based and conventional cytology are acceptable because they have similar test-performance characteristics.
- At an initial visit, providers should ask patients about their recent cytology test and HPV results and any history of evaluation and treatment (e.g., loop electrosurgical excision procedure and colposcopy) to assist with management; effort should be made to obtain copies of recent results. The importance and frequency of screening should be reinforced.

## Counseling

Persons might believe the cytology (Pap test) or HPV test screens for conditions other than cervical cancer, or they might be confused by abnormal results (1252–1254). Health care providers, as trusted sources of information about HPV infections and abnormal cytology test results, have an important role in educating persons about HPV and can moderate the psychosocial impact of abnormal results (1255,1256). Persons should be counseled on the risks, uncertainties, and benefits of screening (174,1257).

An abnormal cytology test or a positive HPV test can cause short-term anxiety, stress, fear, and confusion, possibly decreasing the patient's ability to absorb and retain information and acting as a barrier to follow-up care (1258–1261). A positive HPV test might elicit concerns about partners, worries about disclosure, and feelings of guilt, anger, and stigmatization (1260). Providers should frame HPV positivity in a neutral, nonstigmatizing context and emphasize its common, asymptomatic, and transient nature. Providers also should emphasize that HPV infections often are shared between partners but it is often not possible to know the origin of an HPV infection; HPV tests might become positive many years after initial exposure due to reactivation of latent infections in both male and female partners. Having an HPV infection should not raise concerns about a male partner's health (1262). Providers should communicate the meaning of both the cytology and HPV test results to patients at screening.

Providers also should screen for tobacco use and perform cessation counseling ([www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/09/tobacco-use-and-womens-health](http://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/09/tobacco-use-and-womens-health)). Smoking contributes to the progression of CIN, with both active and passive smoking associated with squamous cell carcinoma of the cervix in women with HPV 16 or 18 infection (1263–1266).

## Promoting Cervical Cancer Screening

Clinics can use the evidence-based interventions in the *Community Preventive Services Task Force* guidelines to promote cervical cancer screening in their communities (<https://www.thecommunityguide.org/findings/cancer-screening-multicomponent-interventions-cervical-cancer>). Implementing interventions that increase community demand for screening (1266) (e.g., client reminders, client incentives, media, group education, or one-on-one education) together with those that increase community access to screening (e.g., reducing structural barriers and reducing client out-of-pocket costs) is effective in increasing cervical cancer screening coverage. These interventions are more effective if they are implemented with interventions to increase provider delivery of screening services (e.g., provider assessment and feedback, provider incentives, and provider reminders). Print materials and online resources are available at [https://www.cdc.gov/cancer/cervical/basic\\_info/screening.htm](https://www.cdc.gov/cancer/cervical/basic_info/screening.htm) and <https://www.cdc.gov/std/hpv/facts-brochures.htm>. Patient navigators can be effective in improving both screening and follow-up after abnormal results (1267).

## Key Messages About Cervical Cancer Screening

When counseling persons about cervical cancer screening, the provider should discuss the following:

- Cervical cancer can be prevented with regular screening tests, like the Pap test (cytology) and HPV tests. Those at average risk should start getting cytology tests at age 21 years.
- The cytology test can find abnormal cervical cells, which could lead to cervical cancer over time, and an HPV test detects HPV infection of the cervix. The HPV test can be used alone for cervical cancer screening or at the same time as the cytology test (known as cotesting) for those aged ≥30 years to 65 years. The HPV test is also used after a cytology test result of atypical squamous cells of undetermined significance (ASC-US) among persons aged >25 years (known as reflex HPV testing).
- Positive cytology and HPV tests are markers of cervical precancerous lesions, which often do not cause symptoms until they become invasive. Appropriate follow-up is essential to ensure that cervical cancer does not develop.
- HPV is a common infection and is often controlled by the body without any medical interventions. A positive HPV test does not mean that a person has cancer.
- Providers should emphasize that HPV infections often are shared between partners, and it is often not possible to know the origin of an HPV infection; HPV tests might become positive many years after initial exposure due to reactivation of latent infections in both male and female partners.

## Management of Sex Partners

The benefit of disclosing a positive HPV test to current and future sex partners is unclear. The following counseling messages can be communicated to sex partners:

- Sex partners do not need to be tested for HPV.
- Sex partners tend to share HPV. Sex partners of persons with HPV infection also are likely have an HPV infection.
- Female sex partners of men who disclose they had a previous female partner with HPV should be screened at the same intervals as women with average risk. No data are available to suggest that more frequent screening is of benefit.
- When used correctly and consistently, condoms might lower the risk for HPV infection and might decrease the time to clear in those with HPV infection. However, HPV can infect areas not covered by the condom, and condoms might not fully protect against HPV (24,25).

Additional messages for partners include the messages for persons with HPV (see Cervical Cancer Screening; Counseling Messages).

## Screening Recommendations in Special Populations

### Pregnancy

Persons who are pregnant should be screened at the same intervals as those who are not. A swab, Ayre's spatula, or cytobrush can be used for obtaining cytology test samples during pregnancy (1268–1270).

### HIV Infection

Several studies have documented an increased risk for cervical precancers and cancers in individuals with HIV infection (1271–1273). Adolescents with HIV should be screened 1 year after onset of sexual activity but no later than age 21 years. Sexually active persons should be screened at the time of the initial HIV diagnosis. Conventional or liquid-based cytology (Pap test) should be used as primary HPV testing and is not recommended in individuals with HIV. Cotesting (cytology and HPV test) can be done in individuals aged ≥30 years with HIV. Annual screening is recommended for persons with HIV infection; after 3 years of consecutive normal cytology results or normal cotest (normal cytology and negative HPV test), the screening interval can be increased to every 3 years. Lifelong screening is recommended among persons with HIV infection.

Providers should defer to existing *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* for guidance on cervical cancer screening and management of results in persons with HIV (98).

## Adolescents

Prevalence of HPV infection is high among those aged <21 years (174); however, HPV infections and squamous intraepithelial lesions caused by HPV in adolescents are more likely to regress than those in older persons. For these reasons, cervical cancer screening and HPV testing are not recommended in immunocompetent adolescents. However, for adolescents with HIV infection, providers should screen 1 year after onset of sexual activity, regardless of age or mode of HIV acquisition (e.g., perinatally acquired or sexually acquired) (98); such screening is warranted because of the reported high rate of progression of abnormal cytology in adolescents with HIV.

## Human Papillomavirus Tests for Cervical Cancer Screening

Clinical tests for HPV are used for the following: cervical cancer screening as a primary test, cervical cancer screening with a cytology test, triage of some abnormal cervical cytology results, follow-up after abnormal screening test results, follow-up after a colposcopy in which no CIN 2 or CIN 3 is found, and follow-up after treatment of cervical precancers. These tests are only FDA cleared for use with cervical specimens, not oral or anal specimens. Testing for nononcogenic HPV types (e.g., types 6 and 11) is not recommended (<https://www.asccp.org/guidelines>).

FDA-cleared HPV tests detect viral DNA or messenger RNA. Several FDA-cleared tests for HPV are available for use in the United States. The Cobas 4800 HPV test (Roche Molecular Diagnostics) and the Onclarity HPV test (Becton Dickinson) can detect the presence of 14 oncogenic HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), as well as individual types 16 and 18, and are cleared for primary cervical cancer screening.

Other HPV tests are cleared for use in conjunction with a cytology test or to triage some abnormal cervical cytology results; they should not be used for primary HPV testing because they are not cleared for this purpose. These tests include the Hybrid Capture 2 High-Risk HPV DNA test (Qiagen), the Cervista HPV High-Risk DNA and HPV 16/18 DNA tests (Hologic), and the APTIMA HR HPV (Gen Probe) test. All HPV assays should be FDA cleared and used only for the appropriate indications (<https://www.fda.gov/media/122799/download>) (158).

HPV testing should not be performed in the following situations:

- Deciding whether to vaccinate against HPV
- Conducting HPV tests for low-risk (nononcogenic) HPV types (e.g., types 6 and 11)
- Providing care to persons with genital warts or their partners

- Testing persons aged <25 years as part of routine cervical cancer screening
- Testing oral or anal specimens

Unlike cytology, samples for HPV testing have the potential to be collected by the patient and mailed to health programs for analysis, thus self-collection might be one strategy for increasing screening rates among populations where screening rates are low. Self-collection for HPV testing is not cleared by FDA or recommended by U.S. medical organizations (174).

## Follow-Up of Abnormal Cytology and Human Papillomavirus Test Results

If the result of the cytology (Pap test) is abnormal, follow-up care should be provided according to the *2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors* (158). Clinics that serve clients who might have difficulty adhering to follow-up recommendations and for whom linkage to care is unlikely should consider offering in-house colposcopy and biopsy services.

Consensus guidelines for management of abnormal cervical cancer screening tests combine patient-level risk data with clinical action thresholds to generate personalized management recommendations (Table 2). This framework allows management on the basis of risk for CIN 3, not specific test results. The guidelines were designed to identify persons at high risk who require colposcopy or expedited treatment and persons at low risk who might be able to safely defer invasive diagnostic procedures. The risk-based framework was designed to easily incorporate future revisions, such as the inclusion of new technologies for screening and management. Use of the guidelines can be facilitated by electronic technology that is continually updated, such as a smartphone application or the website (<https://www.asccp.org/Default.aspx>).

The following are highlights of the new management guidelines:

- Colposcopy can be deferred for patients at low risk.
  - If a patient has a minimally abnormal test result (i.e., negative for intraepithelial lesion or malignancy HPV positive, ASC-US HPV positive, LSIL, or HPV positive) that was preceded by a negative screening HPV test or cotest within the past 5 years, follow-up in 1 year instead of colposcopy is recommended (a negative HPV test or cotest performed during follow-up of abnormal results would not similarly reduce risk).
  - Referral to colposcopy is recommended if cytology test results are abnormal or the HPV test is positive at the 1-year follow-up visit.
- Treatment can be expedited for high-risk patients.
  - If a patient has a high-grade cytology (Pap test) result (i.e., HSIL) and an HPV test that is positive for HPV type 16, then treatment with a loop electrosurgical

**TABLE 2. Comparison of 2012 and 2019 consensus recommendations for management of common abnormalities — American Society for Colposcopy and Cervical Pathology**

Current HPV result	Current Pap test result	Previous result	Management by 2012 guidelines	Management by 2019 guidelines
Negative	ASC-US	Unknown or HPV negative*	Repeat Pap plus HPV testing in 3 yrs	Repeat HPV test with or without concurrent Pap test in 3 yrs
Negative	LSIL	Unknown or HPV negative*	Repeat Pap plus HPV testing in 1 yr preferred, colposcopy acceptable	Repeat HPV test with or without concurrent Pap test in 1 yr
Negative Noncontributory Positive	ASC-H AGC NILM	Noncontributory Noncontributory Unknown or HPV negative*	Colposcopy Colposcopy Repeat Pap plus HPV testing in 1 yr	Colposcopy Colposcopy Repeat HPV test with or without concurrent Pap test in 1 yr
Positive Positive for genotype HPV 16, HPV 18, or both	NILM NILM	HPV positive <sup>†</sup> Noncontributory	Colposcopy Colposcopy	Colposcopy Colposcopy
Positive for genotype HPV 16, HPV 18, or both	ASC-US or LSIL	Noncontributory	Not applicable, genotyping not recommended for ASC-US or LSIL in 2012	Colposcopy
Positive Positive	ASC-US or LSIL ASC-US or LSIL	Unknown or HPV positive Negative screening results with HPV testing or HPV plus Pap testing within the previous 5 yrs	Colposcopy Colposcopy	Colposcopy Repeat HPV test with or without concurrent Pap test in 1 yr <sup>§</sup>
Positive	ASC-US or LSIL	Colposcopy confirming the absence of high-grade lesion within the past yr	Colposcopy	Repeat HPV test with or without concurrent Pap test in 1 yr <sup>§</sup>
Positive	ASC-H	Noncontributory	Colposcopy	Colposcopy or expedited treatment
Positive untyped, positive for genotype other than HPV 16, or negative	HSIL	Noncontributory	Colposcopy or expedited treatment	Colposcopy or expedited treatment
Positive for genotype HPV 16	HSIL	Noncontributory	Colposcopy or expedited treatment	Expedited treatment <sup>¶</sup>

**Sources:** Massad LS, Einstein MH, Huh WK, et al.; 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol* 2013;121:829–46; Perkins RB, Guido RS, Castle PE, et al; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2020;24:102–31; Perkins R, Guido R, Saraiya M, et al. Summary of current guidelines for cervical cancer screening and management of abnormal test results: 2016–2020. *J Womens Health (Larchmt)* 2021;30:5–13.

**Abbreviations:** AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesion or malignancy; Pap = Papanicolaou.

\* Colposcopy may be warranted for patients with a history of high-grade lesions (CIN 2 or CIN 3, histologic or cytologic HSIL, ASC-H, AGC, or AIS).

† Previous Pap test results do not modify the recommendation; colposcopy is always recommended for two consecutive HPV-positive tests.

§ Negative HPV test or cotest (HPV plus Pap test) results only reduce risk sufficiently to defer colposcopy if performed for screening purposes within the last 5 years.

Colposcopy is still warranted if negative HPV test or cotest results occurred in the context of surveillance for a previous abnormal result.

¶ Expedited treatment is preferred for nonpregnant patients aged ≥25 years. Colposcopy with biopsy is an acceptable option if desired by patient after shared decision-making.

- excision procedure (LEEP) is preferred. A colposcopy with biopsy is not necessary to confirm the diagnosis first.
- If a patient who has not been screened in more than 5 years (i.e., rarely screened) has an HSIL cytology result and a positive HPV test (regardless of type), then treatment with LEEP is preferred. A colposcopy with biopsy is not necessary to confirm the diagnosis first.
- When considering treatment without confirmatory biopsy, shared decision-making with the patient is important. Considerations include age, concern about cancer, ability to follow up, financial concerns, and concerns about the potential effect of treatment on a future pregnancy.

- When primary HPV testing is used for screening, cytology testing should be performed for all positive HPV test results to help determine the next steps in management.
- Ideally, cytology testing should be performed by the laboratory as a reflex test from the same specimen so the patient does not need to return to the clinic. Colposcopy is recommended if HPV genotyping is positive for types 16 or 18, and it can be considered if it is infeasible for the patient to return for cytology alone (1274).
- HPV 16 is the highest-risk HPV type. Expedited treatment should be considered for HSIL cytology results, and colposcopy is recommended in all other cases, even if the cytology test is normal.
- HPV 18 has a relatively high association with cancer, and colposcopy is recommended in all cases, even if the

- cytology test is normal. Because of the association of HPV 18 with adenocarcinoma, endocervical sampling is acceptable at the time of colposcopy.
- If the HPV type is not HPV 16 or 18, and the cytology test is normal, return in 1 year is recommended in most cases.
  - HPV testing or cotesting is preferred to cytology testing alone for follow-up after an abnormal test result.
    - Negative HPV testing or cotesting is less likely to miss disease than normal cytology testing alone. Therefore, cytology testing is recommended more often than HPV testing or cotesting for follow-up of abnormal results. Specifically, cytology testing is recommended annually when HPV testing or cotesting is recommended at 3-year intervals, and cytology testing is recommended at 6-month intervals when HPV testing or cotesting is recommended annually.
  - After treatment for a high-grade precancer (moderate or severe dysplasia), surveillance should continue for at least 25 years.
    - Initial testing includes an HPV test or cotest at 6, 18, and 30 months. If cytology alone is used, testing should occur at 6, 12, 18, 24, and 30 months.
    - After completing initial testing, long-term surveillance includes testing at 3-year intervals if using HPV testing or cotesting, or annual testing if using cytology testing alone.
    - Surveillance should continue for at least 25 years after the initial treatment, even if this extends beyond age 65 years. If a woman undergoes hysterectomy during the surveillance period, vaginal screening should continue.

## Anal Cancer

Anal cancer is rare in the general population (1–2 cases per 100,000 person-years); however, incidence is substantially higher among specific populations, including MSM with HIV infection (80–131 cases per 100,000 person-years), men with HIV infection (40–60 cases per 100,000 person-years), women with HIV infection (20–30 cases per 100,000 person-years), and MSM without HIV infection (14 cases per 100,000 person-years) (1275–1279). Incidence is variable among women with previous HPV-related gynecologic dysplasia and cancer (6–63 cases per 100,000 person-years) (1280,1281). Persistent HPV infection might be a risk factor for preventable HPV-associated second primary cancers among survivors of HPV-associated cancers (1282).

Data are insufficient to recommend routine anal cancer screening with anal cytology in persons with HIV infection, MSM without HIV infection, and the general population. An annual digital anorectal examination (DARE) might be useful to detect masses on palpation in persons with HIV infection and possibly in MSM without HIV with a history of receptive

anal intercourse (98). More evidence is needed concerning the natural history of anal intraepithelial neoplasia, the best screening methods and target populations, the safety and response to treatments, and other programmatic considerations before screening can be routinely recommended.

## Populations at High Risk and Digital Anorectal Examination

Providers should discuss anal cancer risk with their patients among specific populations to guide management. According to the HIV Opportunistic Infection guidelines and the International Anal Neoplasia Society, a DARE should be performed to detect early anal cancer in persons with HIV infection and MSM without HIV with a history of receptive anal intercourse (98,1283). DARE is acceptable to patients and has a low risk for adverse outcomes (1284,1285).

Data are insufficient to guide initiation of DARE at a defined age or optimal intervals for examination. Whereas anal HSIL is observed among young adults, cancer incidence begins to increase after the early 30s and continues to increase as a function of age.

## Populations at High Risk and Anal Cytology

Data are insufficient to recommend routine anal cancer screening with anal cytology among populations at risk for anal cancer. Certain clinical centers perform anal cytology to screen for anal cancer among populations at high risk (e.g., persons with HIV infection, MSM, and those having receptive anal intercourse), followed by high-resolution anoscopy (HRA) for those with abnormal cytologic results (e.g., ACS-US, LSIL, or HSIL). Sensitivity and specificity of anal cytology to detect HSIL are limited (sensitivity 55%–89% and specificity 40%–67%) (1286–1291). Health centers that initiate a cytology-based screening program should only do so if referrals to HRA and biopsy are available.

HRA can be used for diagnosis of HSIL, to monitor response to therapy, or to conduct surveillance of HSIL for evidence of progression. HRA is the primary method used for diagnosis of superficially invasive squamous carcinoma, a very early form of anal cancer that is not palpable on DARE. However, data are insufficient to conclude whether use of HRA leads to reductions in anal cancer incidence or improves anal cancer morbidity and mortality. An ongoing clinical trial is investigating whether treatment of HSIL is effective in reducing the incidence of anal cancer among persons with HIV infection (NCT02135419).

## Human Papillomavirus Testing

HPV tests (using high-risk HPV types) are not clinically useful for anal cancer screening because of a high prevalence of anal HPV infection among populations at high risk, particularly MSM (1278,1289,1290). No standard HPV-based

algorithms exist for anal cancer screening due to the high prevalence of high-risk HPV infection among groups at risk.

### Treatment of Anal High-Grade Squamous Intraepithelial Lesion

Multiple office-based treatments exist for anal HSIL, including ablative methods (e.g., laser, electrocautery, or infrared coagulation) and topical patient-applied therapies (e.g., imiquimod). Recurrence rates with both provider-applied and patient-applied treatments are high, ranging from approximately 50% at 1 year to 77% after 3 years (1289,1292,1293). In addition, evidence exists that HSIL might spontaneously regress without treatment (1294,1295). Shared decision-making about treatment for anal HSIL is recommended because of limited data on the natural history of anal HSIL, including factors related to progression or regression of lesions.

## Viral Hepatitis

### Hepatitis A Virus Infection

HAV infection has an incubation period of approximately 28 days (range: 15–50 days) (1296). HAV replicates in the liver and is shed in high concentrations in feces from 2–3 weeks before to 1 week after the onset of clinical illness. HAV infection produces a self-limited disease that does not result in chronic infection or chronic liver disease. However, approximately 10% of patients experience a relapse of symptoms during the 6 months after acute illness. Acute liver failure from hepatitis A is rare (overall case-fatality rate: 0.5%). The risk for symptomatic infection is directly related to age, with approximately 70% of adults having symptoms compatible with acute viral hepatitis and the majority of children having either asymptomatic or unrecognized infection. Antibody produced in response to HAV infection persists for life and confers protection against reinfection (1297).

HAV infection is primarily transmitted by the fecal-oral route, by either person-to-person contact or through consumption of contaminated food or water (1298). Transmission of HAV during sexual activity probably results from fecal-oral contact. Although viremia occurs early during infection and can persist for weeks after symptom onset, bloodborne transmission of HAV is uncommon (1299). Transmission by saliva has not been demonstrated.

In the United States, of the hepatitis A cases accompanied by risk information, a particular risk was identified among only 23.8% (13,372). Among cases with a risk factor identified, a recognized foodborne or waterborne outbreak was the most commonly identified risk (49.6%). Other infection sources

identified in the United States include MSM; persons who use injecting drugs; sexual and household contacts; those experiencing homelessness; international travelers; those with children attending a nursery, childcare, or preschool; and persons working in such settings (13,372).

### Diagnostic Considerations

Diagnosis of HAV infection cannot be made on a clinical basis alone but requires serologic testing. Presence of IgM antibody to HAV is diagnostic of acute HAV infection. A positive test for total anti-HAV indicates immunity to HAV infection but does not differentiate current from previous HAV infection. Although usually not sensitive enough to detect the low level of protective antibody after vaccination, anti-HAV tests also might be positive after hepatitis A vaccination.

### Treatment

Patients with acute HAV infection usually require only supportive care, with no restrictions in diet or activity. Hospitalization might be necessary for patients who become dehydrated because of nausea and vomiting and is crucial for patients with signs or symptoms of acute liver failure. Medications that might cause liver damage or are metabolized by the liver should be used with caution among persons with HAV infection.

### Prevention

Vaccination is the most effective means of preventing HAV transmission among persons at risk for infection (e.g., MSM, injecting drug users, and persons with chronic liver disease) who did not receive hepatitis A vaccination during childhood. Hepatitis A vaccines are prepared from formalin-inactivated, cell-culture-derived HAV. Two monovalent vaccines (Havrix and Vaqta are approved by FDA for persons aged ≥12 months (Table 3). These vaccines are available for eligible children and adolescents aged <19 years through the VFC program (<https://www.cdc.gov/vaccines/programs/vfc/index.html>). Administered IM in a 2-dose series at 0 and 6–12 months, hepatitis A vaccines induce protective antibody levels among virtually all adults. By 1 month after the first dose, 94%–100% of adults have protective antibody levels, and after a second dose, 100% achieve protective levels (1297,1300,1301). Kinetic models of antibody decrease among adults indicate that protective levels persist for >40 years (1302–1304). A study of Alaska Natives demonstrated that seropositivity for hepatitis A persists for >20 years after completing 2-dose vaccination at age 12–21 months (1302). Anti-HAV persistence of >20 years was demonstrated among immunocompetent adults vaccinated with a 2-dose hepatitis A schedule as adults (1303,1305). A combined hepatitis A and hepatitis B vaccine (Twinrix) has

been developed and licensed for use as a 3-dose series for adults aged ≥18 years at risk for HAV or HBV infections. When administered IM on a 0-, 1-, and 6-month schedule, the vaccine has equivalent immunogenicity to that of the monovalent hepatitis A vaccines.

### Pre-Exposure Vaccination

Persons at risk for HAV infection (Box 5) (1297) should be offered vaccine (Table 3). If persons are at risk for both HAV and HBV, the combined vaccine can be considered.

### Prevaccination Serologic Testing

Among U.S.-born adults aged >20 years, HAV susceptibility prevalence (i.e., total antibody to HAV was negative) was 74.1% (95% CI: 72.9%–75.3%) during 2007–2016 (1306). Prevaccination serologic testing for HAV immunity before vaccination is not routinely recommended; however, it can be considered in specific settings to reduce costs by not vaccinating persons who are already immune. Prevaccination serologic testing should not be a barrier to vaccination of susceptible persons, especially for populations that are difficult to access. If prevaccination testing is performed, commercially available tests for total anti-HAV or IgG anti-HAV should be used (1297).

**TABLE 3. Vaccines for preventing hepatitis A infection**

Vaccine	Trade name (manufacturer)	Age group (yrs)	Dose	Route	Schedule	Booster
Hep A inactivated (2 doses)	Havrix (GlaxoSmithKline)	1–18	0.5 mL (720 ELISA units inactivated HAV)	IM	0, 6–12 mos	None
		≥19	1 mL (1,440 ELISA units inactivated HAV)	IM	0, 6–12 mos	None
Hep A inactivated (2 doses)	Vaqta (Merck)	1–18	0.5 mL (25 units HAV antigen)	IM	0, 6–18 mos	None
		≥19	1 mL (50 units HAV antigen)	IM	0, 6–18 mos	None
Combined Hep A and Hep B* (3 doses)	Twinrix (GlaxoSmithKline)	≥18 (primary)	1 mL (720 ELISA units inactivated plus 20 µg HBsAg)	IM	0, 1, 6 mos	None
		≥18 (accelerated)	1 mL (720 ELISA units inactivated plus 20 µg HBsAg)	IM	0, 7, 21–30 days	12 mos

**Source:** Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69(No. RR-5).

**Abbreviations:** ELISA = enzyme-linked immunosorbent assay; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; Hep A = hepatitis A; Hep B = hepatitis B; IM= intramuscular.

\* Combined Hep A and Hep B vaccine (Twinrix) should not be used as postexposure prophylaxis.

### BOX 5. Populations recommended for hepatitis A vaccination — Advisory Committee on Immunization Practices, 2020

#### Children

- All children aged 12–23 months
- Unvaccinated children and adolescents aged 2–18 years

#### Persons at increased risk for hepatitis A virus (HAV) infection

- International travelers
- Men who have sex with men
- Persons who use injecting or noninjecting drugs (i.e., all those who use illegal drugs)
- Persons with occupational risk for exposure
- Persons who anticipate close personal contact with an international adoptee
- Persons experiencing homelessness

#### Persons at increased risk for severe disease from HAV infection

- Persons with chronic liver disease
- Persons with HIV infection

#### Other persons recommended for vaccination

- Pregnant women at risk for HAV infection or severe outcome from HAV infection
- Any persons who requests a vaccine

#### Vaccination during outbreaks

- Unvaccinated persons in outbreak settings who are at risk for HAV infection or at risk for severe disease from HAV

#### Implementation strategies for settings providing services to adults

- Persons in settings that provide services to adults where a high proportion of those persons have risk factors for HAV infection

#### Hepatitis A vaccination is no longer recommended by the Advisory Committee on Immunization Practices

- Persons who receive blood products for clotting disorders (e.g., hemophilia)

**Source:** Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69(No. RR-5).

Persons for whom prevaccination testing will likely be most cost-effective include adults who were either born in or lived for extensive periods in geographic areas where HAV endemicity is high or intermediate (1297). Prevaccination serologic testing of children is not indicated because of the low prevalence of infection among that age group.

For populations who are expected to have high rates of previous HAV infection, vaccination history should be obtained when feasible before testing or vaccination. Vaccination should not be postponed if vaccination history cannot be obtained, records are unavailable, or prevaccination testing is infeasible. Vaccinating persons immune from natural infection carries no known risk, nor does giving extra doses of hepatitis A vaccine (1307). Vaccination of a person who is already immune is not harmful. Persons who have a documented history of ≥2 doses of hepatitis A vaccine do not need further vaccination or serologic testing.

### Postvaccination Serologic Testing

Serologic testing for immunity is unnecessary after routine vaccination of infants, children, or adults (1297). Testing for anti-HAV antibody after vaccination is recommended for persons whose subsequent clinical management depends on knowledge of their immune status and persons for whom revaccination might be indicated (e.g., persons with HIV infection and other immunocompromising conditions).

### Postexposure Prophylaxis

Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of monovalent hepatitis A vaccine or immunoglobulin (IG) (0.1 mL/kg body weight) as soon as possible, ideally <2 weeks after exposure because the efficacy of vaccine or IG when administered >2 weeks after exposure has not been established (1297). In most cases, monovalent hepatitis A vaccine at the age-appropriate dose is preferred over IG for PEP. Advantages of hepatitis A vaccine for PEP include induction of active immunity, longer-term protection, ease of administration, and better acceptability and availability. Decisions to use vaccine versus IG should be guided by patient characteristics associated with more severe manifestations of HAV infection (e.g., older age, immunocompromising conditions, and chronic liver disease) and the magnitude of the risk for HAV transmission resulting from the exposure (1297).

IG should be used for children aged <6 months, immunocompromised persons, persons with chronic liver disease, and persons for whom vaccine is contraindicated. IG can be administered to persons aged >40 years, in addition to hepatitis A vaccine (1297).

IG administered IM can provide PEP against HAV (Table 4). IG is a sterile solution of concentrated immunoglobulins prepared

**TABLE 4. Recommendations for hepatitis A postexposure prophylaxis and pre-exposure protection, by age group and risk category — Advisory Committee on Immunization Practices, 2020**

Indication and age group	Risk category and health status	Hepatitis A vaccine	IG*
<b>Postexposure prophylaxis</b>			
0–11 mos	Healthy	No	0.1 mL/kg body weight
12 mos to 40 yrs	Healthy	1 dose†	None
>40 yrs	Healthy	1 dose†	0.1 mL/kg body weight§
≥12 mos	Immunocompromised or chronic liver disease	1 dose†	0.1 mL/kg body weight¶
≥12 mos	Vaccine contraindicated**	No	0.1 mL/kg body weight
<b>Pre-exposure protection (e.g., travel)††</b>			
<6 mos	Healthy	No	0.1–0.2 mL/kg body weight§§
6–11 mos	Healthy	1 dose¶¶	None
12 mos to 40 yrs	Healthy	1 dose***	None
>40 yrs	Healthy	1 dose***	0.1–0.2 mL/kg body weight§§,†††
>6 mos	Immunocompromised or chronic liver disease	1 dose***	0.1–0.2 mL/kg body weight§§,†††
>6 mos	Persons who elect not to receive vaccine or for whom vaccine is contraindicated**	No	0.1–0.2 mL/kg body weight§§

**Source:** Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69(No. RR-5).

**Abbreviations:** HAV = hepatitis A virus; IG = immune globulin.

\* Measles, mumps, and rubella vaccine should not be administered for ≥2 weeks before and 6 months after administration of IG.

† A second dose of hepatitis A vaccine is not required for postexposure prophylaxis; however, for long-term immunity, the vaccination series should be completed with a second dose ≥6 months after the first dose.

§ The provider's risk assessment should determine the need for IG administration. If the provider's risk assessment determines that both vaccine and IG are warranted, hepatitis A vaccine and IG should be administered simultaneously at different anatomic sites (e.g., separate limbs).

¶ Vaccine and IG should be administered simultaneously at different anatomic sites (e.g., separate limbs).

\*\* Life-threatening allergic reaction to a previous dose of hepatitis A vaccine or allergy to any vaccine component.

†† IG should be considered before travel for persons with special risk factors for either HAV infection or severe disease from HAV infection.

§§ 0.1 mL/kg body weight for travel ≤1 month; 0.2 mL/kg body weight for travel ≤2 months; 0.2 mL/kg every 2 months for travel of ≥2 months' duration.

¶¶ This dose should not be counted toward the routine 2-dose series, which should be initiated at age 12 months.

\*\*\* For persons not previously vaccinated with hepatitis A vaccine, administer dose as soon as travel is considered and complete the series according to routine schedule if the next dose is needed before travel.

††† Can be administered on the basis of the provider's risk assessment.

from pooled human plasma processed by cold ethanol fractionation. In the United States, IG is produced only from plasma that has tested negative for HBsAg, antibodies to HIV and HCV, and HIV and HCV RNA. In addition, the process used to manufacture IG inactivates viruses (e.g., HBV, HCV, and HIV). When administered IM <2 weeks after exposure to HAV, IG is >85% effective in preventing HAV infection (1308).

If IG is administered to persons for whom hepatitis A vaccine also is recommended, a dose of vaccine should be provided simultaneously with IG in different anatomic sites (e.g., different limbs) as soon as possible, and the second vaccine dose should be administered according to the licensed schedule to complete the series. The combined vaccine can be considered for persons among whom both hepatitis A and hepatitis B vaccine is recommended (13,1297,1302–1304).

## Special Considerations

For persons with HIV infection, antibody response can be directly related to CD4<sup>+</sup> T-cell levels. Although persons with HIV who have lower CD4<sup>+</sup> T-cell counts or percentages might have a weaker response to the vaccine, vaccination should not be delayed for the CD4<sup>+</sup> T-cell count to exceed a certain threshold because of the prolonged risk for HAV exposure created by missed opportunities to vaccinate.

## Hepatitis B Virus Infection

The incubation period for HBV infection from time of exposure to symptom onset ranges from 6 weeks to 6 months. The highest concentrations of HBV are located in blood, with lower concentrations in other body fluids including wound exudates, semen, vaginal secretions, and saliva (1309,1310). HBV is more infectious and more stable in the environment than other bloodborne pathogens (e.g., HCV or HIV).

HBV infection can be either self-limited or chronic. Among adults, approximately half of newly acquired HBV infections are symptomatic, and approximately 1% of reported cases result in acute liver failure and death (1311). Risk for chronic infection is inversely related to age at acquisition; approximately 90% of infected infants and 30% of infected children aged <5 years become chronically infected, compared with 2%–6% of persons who become infected as adults (1312). Among persons with chronic HBV infection, the risk for premature death from cirrhosis or hepatocellular carcinoma is 15%–25% (1313).

HBV is efficiently transmitted by percutaneous or mucous membrane exposure to HBV-infected blood or body fluids that contain HBV. The primary risk factors associated with infection among adolescents and adults are unprotected sex with an infected partner, having multiple partners, men having

sex with men, having history of other STIs, and injecting drug use (233). In addition, studies have demonstrated other modes of HBV transmission, including premaritalation and lapses in health care infection control procedures, as less common sources of transmission (1314–1317).

CDC's national strategy for eliminating transmission of HBV infection includes prevention of perinatal infection through routine screening of all pregnant women for HBsAg and immunoprophylaxis of infants born to mothers with HBsAg or mothers whose HBsAg status is unknown, routine infant vaccination, vaccination of previously unvaccinated children and adolescents through age 18 years, and vaccination of previously unvaccinated adults at increased risk for infection (12). High vaccination coverage rates with subsequent decreases in acute HBV infection incidence have been achieved among infants and adolescents (1318). The vaccination of persons as children and adolescents likely has led to improved vaccination coverage among adults aged <30 years (1319) and corresponding lower rates of acute HBV infection among this group. In contrast, vaccination coverage among the majority of adult populations at high risk aged ≥30 years (e.g., persons with multiple sex partners, MSM, and injecting drug users) has remained low (1320,1321); these groups account for the highest rates of preventable acute infections (12,1319,1322). STD clinics and other health care settings providing STI services to adults at high risk for infection should administer hepatitis B vaccine to those who are unvaccinated.

## Diagnosis

Diagnosis of acute or chronic HBV infection requires serologic testing (Table 5). Because HBsAg is present in both acute and chronic infection, presence of IgM antibody to hepatitis B core antigen (IgM anti-HBc) is diagnostic of acute or recently acquired HBV infection. Antibody to HBsAg (anti-HBs) is produced after a resolved infection and is the only HBV antibody marker present after vaccination. The presence of HBsAg and anti-HBc, with a negative test for IgM anti-HBc, indicates chronic HBV infection. The presence of total anti-HBc alone might indicate acute, resolved, or chronic infection or a false-positive result.

## Treatment

No specific therapy is available for persons with acute HBV infection; treatment is supportive. Persons with chronic HBV infection should be referred for evaluation to a provider experienced in managing such infections. Therapeutic agents approved by FDA for treatment of chronic HBV infection can achieve sustained suppression of HBV replication and remission of liver disease (1323).

**TABLE 5. Interpretation of serologic test results\* for hepatitis B virus infection**

Serologic marker				Interpretation
HBSAG	Total anti-HBc	IgM anti-HBc	Anti-HBs	
—	—	—	—	Never infected
+†	—	—	—	Early acute infection; transient ( $\leq 18$ days) after vaccination
+	+	+	—	Acute infection
—	+	+	—	Acute resolving infection
—	+	—	+	Recovered from past infection and immune
+	+	—	—	Chronic infection
—	+	—	—	Past infection; low-level chronic infection§; passive transfer to infant born to HBsAg-positive mother; false positive (no infection)
—	—	—	+	Immune if concentration is $>10$ mIU/mL after vaccination, passive transfer after HBIG administration

**Source:** Adapted from Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1).

**Abbreviations:** anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M.

\* — = negative test result; + = positive test result.

† To ensure that an HBsAg-positive test result is not false positive, samples with repeatedly reactive HBsAg results should be tested with a neutralizing confirmatory test cleared by the Food and Drug Administration.

§ Persons positive for only anti-HBc are unlikely to be infectious, except under unusual circumstances involving direct percutaneous exposure to large quantities of blood (e.g., blood transfusion or organ transplantation) or mutant HBsAg-related infection.

## Prevention

Two products have been approved for HBV prevention: hepatitis B immune globulin (HBIG) for PEP and hepatitis B vaccine (12). HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination. HBIG is prepared from plasma known to contain high concentrations of anti-HBs. The recommended dose of HBIG is 0.06 mL/kg body weight.

Hepatitis B vaccine contains HBsAg produced in yeast by recombinant DNA technology and provides protection from HBV infection when used for both pre-exposure vaccination and PEP. The three available monovalent hepatitis B vaccines for use in the United States are Recombivax HB, Engerix-B, and Heplisav-B. A combination hepatitis A and hepatitis B vaccine for use among persons aged  $\geq 18$  years, Twinrix, also is available.

When selecting a hepatitis B vaccination schedule, health care providers should consider the need to achieve completion of the vaccine series. The recommended HBV dose and schedule varies by product and age of recipient (Table 6). Three different 3-dose schedules for adolescents and adults have been approved for both monovalent hepatitis B vaccines (i.e., Engerix-B and Recombivax HB); these vaccines can be administered at 0, 1, and 6 months; 0, 1, and 4 months; or 0, 2, and 4 months. A 4-dose schedule of Engerix-B at 0, 1, 2, and 12 months is licensed for all age groups. A 2-dose schedule of Recombivax HB adult formulation (10  $\mu$ g) is licensed for adolescents aged 11–15 years, with a 4-month minimal interval between doses. When scheduled to receive the second dose, adolescents

aged 16–19 years should be switched to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation (5  $\mu$ g) administered on a recommended schedule. Heplisav-B is a new single-antigen recombinant hepatitis B vaccine with a novel cytosine-phosphate-guanine 1018 oligodeoxynucleotide adjuvant for prevention of HBV infection among persons aged  $\geq 18$  years, administered as a 2-dose series at 0 and 1 month (>4 weeks apart) (156). Twinrix is a 3-dose schedule administered at 0, 1, and 6 months to persons aged  $\geq 18$  years at risk for both HAV and HBV infections.

Hepatitis B vaccine should be administered IM in the deltoid muscle and can be administered simultaneously with other vaccines. If the vaccine series is interrupted after the first or second dose of vaccine, the missed dose should be administered as soon as possible. The series does not need to be restarted after a missed dose. HBV vaccination is available for eligible children and adolescents aged <19 years through the VFC program (<https://www.cdc.gov/vaccines/programs/vfc/contacts-state.html>). When feasible, the same manufacturer's vaccines should be used to complete the series; however, vaccination should not be deferred when the manufacturer of the previously administered vaccine is unknown or when the vaccine from the same manufacturer is unavailable (1324).

Among adolescents and healthy adults aged <40 years, approximately 30%–55% achieve a protective antibody response (i.e., anti-HBs  $\geq 10$  mIU/mL) after the first single-antigen vaccine dose, 75% after the second, and >90% after the third. Recent clinical trials reported a protective antibody response achieved among approximately 90% of participants receiving Heplisav-B, compared with 70.5%–90.2% of participants receiving Engerix-B (12). Vaccine-induced immune memory has been demonstrated to persist for >30 years (1325–1327).

**TABLE 6. Recommended doses of licensed formulations of hepatitis B vaccines**

Age group (yrs)	Single-antigen vaccine				Combination vaccine			
	Recombivax HB		Engerix-B		Heplisav-B*		Twinrix†	
	Dose ( $\mu$ g)‡	Volume (mL)	Dose ( $\mu$ g)‡	Volume (mL)	Dose ( $\mu$ g)‡	Volume (mL)	Dose ( $\mu$ g)‡	Volume (mL)
Infants (<1)	5	0.5	10	0.5	—¶	—¶	NA	NA
Children (1–10)	5	0.5	10	0.5	—¶	—¶	NA	NA
Adolescents (11–15)	10**	1.0	NA	NA	—¶	—¶	NA	NA
Adolescents (11–19)	5	0.5	10	0.5	—¶	—¶	NA	NA
Adults (≥18)	—††	—††	—††	—††	20*	0.5	20†	1
Adults (≥20)	10	1.0	20	1.0	20†	0.5	20†	1
Hemodialysis patients and other immunocompromised persons (<20§§)	5	0.5	10	0.5	20	0.5	NA	NA
Hemodialysis patients and other immunocompromised persons (≥20)	40¶¶	1.0	40***	2.0	20	0.5	NA	NA

**Source:** Adapted from Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1).

**Abbreviation:** NA = not applicable.

\* Administered on a 2-dose schedule.

† Combined hepatitis A and B vaccines. This vaccine is recommended for persons aged ≥18 years who are at increased risk for both hepatitis B and hepatitis A virus infections.

‡ Recombinant hepatitis B surface antigen protein dose.

¶ Heplisav-B should not be used for vaccination of infants, children, or adolescents because the safety and effectiveness of Heplisav-B has not been established in persons aged <8 years and is not approved for use in these populations.

\*\* Adult formulation administered on a 2-dose schedule.

†† Engerix-B and Recombivax HB are approved for use in persons of all ages.

§§ Higher doses might be more immunogenic; however, no specific recommendations have been made.

¶¶ Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.

\*\*\* Two 1.0-mL doses administered at one site, on a 4-dose schedule at 0, 1, 2, and 6 months.

Periodic testing to determine antibody levels after routine vaccination among immunocompetent persons is unnecessary, and booster doses of vaccine are not recommended.

Hepatitis B vaccination is usually well tolerated by the majority of recipients. Pain at the injection site and low-grade fever are reported by a minority of recipients. For children and adolescents, a causal association exists between receipt of hepatitis B vaccination and anaphylaxis. For each 1.1 million doses of vaccine administered, approximately one recipient will experience this type of reaction (1328); however, no deaths have been reported among these patients (1318,1328). Vaccine is contraindicated for persons with a history of anaphylaxis after a previous dose of hepatitis B vaccine and persons with a known anaphylactic reaction to any vaccine component (1329). No other adverse events after administration of hepatitis B vaccine have been demonstrated.

### Pre-Exposure Vaccination

Hepatitis B vaccination is recommended for all unvaccinated children and adolescents; all unvaccinated adults at risk for HBV infection, especially injecting drug users; MSM; adults with multiple sex partners; sex partners, needle-sharing contacts, or household contacts of persons with chronic hepatitis B; and persons with diabetes and all adults seeking protection from HBV infection (1318). For adults, acknowledgment of a specific risk factor is not a requirement for vaccination.

Hepatitis B vaccine should be routinely offered to all unvaccinated persons attending STD clinics and to all unvaccinated persons seeking evaluation or treatment for STIs in other settings, especially correctional facilities, facilities providing substance misuse treatment and prevention services, Federally Qualified Health Centers, and settings serving MSM (e.g., HIV infection care and prevention settings). If hepatitis B vaccine is unavailable at a particular facility, persons should be linked to a setting where they can receive vaccine. Persons with a reliable vaccination history (i.e., a written, dated record of each dose of a complete series) or reliable history of hepatitis B infection (i.e., a written record of infection and serologic results providing evidence of previous infection) do not require vaccination. In all settings, vaccination should be initiated at the initial visit, even if concerns about completion of the vaccine series exist.

### Prevaccination Serologic Testing

Conducting prevaccination serologic testing for susceptibility just before the initial vaccine dose is administered can be considered for identifying persons with chronic HBV infection and, potentially, reducing the cost of completing the vaccination series for adult populations that have an expected high prevalence (20%–30%) of HBV infection (e.g., injecting drug users and MSM, especially those among older age groups, or persons born where HBV endemicity is moderate to high). In addition, prevaccination testing for susceptibility is

recommended for unvaccinated household, sexual, and needle-sharing contacts of HBsAg-positive persons (1318). Serologic testing should not be a barrier to vaccination. The first vaccine dose should be administered immediately after collection of the blood sample for serologic testing. Vaccination of persons who are immune to HBV infection because of current or previous infection or vaccination is not harmful and does not increase the risk for adverse events.

Prevaccination testing should be performed with HBsAg, anti-HBs, and total anti-HBc to define patients' HBV clinical status and deliver recommended care (1330). Persons who test HBsAg positive should receive prevention counseling and evaluation for antiviral treatment (see Management of Persons Who Are HBsAg Positive). Persons who test total anti-HBc positive and anti-HBs positive should be counseled that they have had previous HBV infection and are immune. Those persons with isolated anti-HBc (i.e., negative HBsAg and anti-HBs) need further assessment to rule out occult HBV infection, and they are at higher risk for reactivation if exposed to immunosuppressants. Persons who test negative to all three HBV seromarkers should receive the complete vaccination series, with the first vaccine dose administered immediately.

### **Postvaccination Serologic Testing for Response**

Postvaccination serologic testing for immunity is unnecessary after routine vaccination of adolescents or adults. However, such testing is recommended for persons whose subsequent clinical management depends on knowledge of their immune status. Persons recommended to receive postvaccination serologic testing include health care personnel and public safety workers, persons with HIV infection, sex and needle-sharing partners of HBsAg-positive persons, hemodialysis patients and others who might require outpatient hemodialysis (e.g., predialysis, peritoneal dialysis, or home dialysis), and other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy) (1318).

If indicated, anti-HBs testing should be performed 1–2 months after administration of the last dose of the vaccine series. Persons determined to have anti-HBs levels of <10 mIU/mL after the primary vaccine series should be revaccinated with a 3-dose series and tested again for anti-HBs 1–2 months after the third dose. Persons who do not respond to revaccination should be tested for HBsAg and HBc. If HBsAg positive, persons should receive recommended management (see Management of Persons Who Are HBsAg Positive). If HBsAg negative, persons should be considered susceptible to HBV infection and counseled about precautions for preventing HBV infection and the need for HBIG PEP for any known exposure. If isolated anti-HBc positive (i.e., negative HBsAg and anti-HBs), persons will need further assessment to rule out

occult HBV infection and are at higher risk for reactivation if exposed to immunosuppressants.

### **Postexposure Prophylaxis**

Both passive and active PEP (simultaneous administration of HBIG [i.e., 0.06 mL/kg body weight] and hepatitis B vaccine at separate anatomic sites) and active PEP (administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV (12). HBIG alone also has been demonstrated to be effective in preventing HBV transmission; however, with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination.

### **Exposure to a Source Who Is HBsAg Positive**

Unvaccinated persons or persons known not to have responded to a complete hepatitis B vaccine series should receive both HBIG and hepatitis vaccine as soon as possible (preferably ≤24 hours) after a discrete, identifiable exposure to blood or body fluids that contain blood from a person with HBsAg (Table 7). Hepatitis B vaccine should be administered simultaneously with HBIG at a separate anatomic site, and the vaccine series should be completed by using the age-appropriate vaccine dose and schedule (Table 6). Exposed persons who are not fully vaccinated because they have not completed the vaccine series should receive HBIG (i.e., 0.06 mL/kg body weight) and complete the vaccine series. Persons who have written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing should receive a single vaccine booster dose. Exposed persons who are known to have responded to vaccination by postvaccination testing are considered protected; therefore, they need no additional doses of vaccine or HBIG. All persons with an occupational exposure to blood or body fluids that contain HBV should be managed according to guidelines (12).

### **Exposure to a Source with Unknown HBsAg Status**

Unvaccinated persons and persons with previous nonresponse to hepatitis B vaccination who have a discrete, identifiable exposure to blood or body fluids containing blood from a person with unknown HBsAg status should receive the hepatitis B vaccine series, with the first dose initiated as soon as possible after exposure (preferably <24 hours) and the series completed according to the age-appropriate dose and schedule. Exposed persons who are not fully vaccinated but started the series should complete the vaccine series. Exposed persons with written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing require no further treatment.

**TABLE 7. Guidelines for postexposure prophylaxis\* of persons with nonoccupational exposure<sup>†</sup> to blood or body fluids that contain blood, by exposure type and hepatitis B vaccination status**

Source of exposure	Unvaccinated person <sup>§</sup>	Previously vaccinated person <sup>¶</sup>
<b>HBsAg-positive source</b> Percutaneous (e.g., bite or needlestick) or mucosal exposure to HBsAg-positive blood or body fluids <i>or</i> Sex or needle-sharing contact with an HBsAg-positive person <i>or</i> Victim of sexual assault or abuse by an assailant who is HBsAg positive	Administer hepatitis B vaccine series and HBIG	Complete hepatitis B vaccine series and HBIG, if vaccine series not completed <i>or</i> Administer hepatitis B vaccine booster dose, if previous vaccination without testing**
<b>Source with unknown HBsAg status</b> Percutaneous (e.g., bite or needlestick) or mucosal exposure to potentially infectious blood or body fluids from a source with unknown HBsAg status <i>or</i> Sex or needle-sharing contact with person with unknown HBsAg status <i>or</i> Victim of sexual assault or abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine series	Complete hepatitis B vaccine series

**Sources:** CDC. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. MMWR Recomm Rep 2013;62(No. RR-10); CDC. Postexposure prophylaxis to prevent hepatitis B virus infection. MMWR Recomm Rep 2006;55(No. RR-16).

**Abbreviations:** HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen.

\* When indicated, immunoprophylaxis should be initiated as soon as possible, preferably within 24 hours. Studies are limited regarding the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures or 14 days for sexual exposures. The hepatitis B vaccine series should be completed. These guidelines apply to nonoccupational exposures.

† These guidelines apply to nonoccupational exposures.

§ A person who is in the process of being vaccinated but who has not completed the vaccine series should complete the series and receive treatment for hepatitis B as indicated.

¶ A person who has written documentation of a complete hepatitis B vaccine series and who did not receive postvaccination testing.

\*\* No booster dose is needed for persons who have written documentation of hepatitis B vaccine series with serologic response.

## Other Management Considerations

All persons with HBV infection should be tested for HIV, syphilis, gonorrhea, and chlamydia.

## Management of Persons Who Are HBsAg Positive

Recommendations for management of all persons with HBsAg include the following:

- All persons with HBsAg documented on laboratory results should be reported to the state or local health department.
- To verify the presence of chronic HBV infection, persons with HBsAg should be retested. The absence of IgM anti-HBc or the persistence of HBsAg for ≥6 months indicates chronic HBV infection.
- Persons with chronic HBV infection should be referred for evaluation to a specialist experienced in managing chronic hepatitis B infection.
- Household, sexual, and needle-sharing contacts of persons with chronic infection should be evaluated. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing (see Prevaccination Serologic Testing). Susceptible persons

should complete the vaccine series by using an age-appropriate vaccine dose and schedule.

- Sex partners of persons with HBsAg should be counseled to use latex condoms (*1331*) to protect themselves from sexual exposure to infectious body fluids (e.g., semen and vaginal secretions), unless they have been demonstrated to be immune after vaccination (anti-HBs ≥10 mIU/mL) or previously infected (anti-HBc positive).
- To prevent or reduce the risk for transmission to others in addition to vaccination, persons with HBsAg also should be advised to
  - use methods (e.g., condoms) to protect nonimmune sex partners from acquiring HBV infection from sexual activity until the partner can be vaccinated and immunity documented;
  - cover cuts and skin lesions to prevent spread by infectious secretions or blood;
  - refrain from donating blood, plasma, body organs, other tissue, or semen; and
  - refrain from sharing household articles (e.g., toothbrushes, razors, or personal injecting equipment) that could become contaminated with blood, and refrain from pre masturbation of food.
- To protect the liver from further harm, persons with HBsAg should be advised to

- avoid or limit alcohol consumption because of the effects of alcohol on the liver;
- refrain from starting any new medicines, including over-the-counter and herbal medicines, without checking with their health care provider; and
- obtain vaccination against hepatitis A.

When seeking medical or dental care, persons who are HBsAg positive should be advised to inform their health care providers of their HBsAg status so that they can be evaluated and managed. The following are key counseling messages for persons with HBsAg:

- HBV is not usually spread by hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact.
- Persons should not be excluded from work, school, play, childcare, or other settings because they are infected with HBV.
- Involvement with a support group might help patients cope with chronic HBV infection.
- HBV infection is a chronic condition that can be treated, and patients should receive prevention counseling and be evaluated for antiviral treatment.

## Special Considerations

### Pregnancy

Regardless of whether they have been previously tested or vaccinated, all pregnant women should be tested for HBsAg at the first prenatal visit and again at delivery if at high risk for HBV infection (see STI Detection Among Special Populations). Pregnant women at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination. All pregnant women with HBsAg should be reported to state and local perinatal hepatitis B prevention programs and referred to a specialist. Information about management of pregnant women with HBsAg and their infants is available at <https://www.cdc.gov/hepatitis/hbv/perinatalxmtn.htm>.

### HIV Infection

HIV infection can impair the response to hepatitis B vaccination. Persons with HIV should be tested for anti-HBs 1–2 months after the third vaccine dose (see Postvaccination Serologic Testing). Modified dosing regimens, including a doubling of the standard antigen dose and administration of additional doses, might increase the response rate and should be managed in consultation with an infectious disease specialist. Additional recommendations for management of persons with HBsAg and HIV infection are available (98).

## Hepatitis C Virus Infection

HCV infection is the most common chronic bloodborne infection in the United States, with an estimated 2.4 million persons living with chronic infection (1332). HCV is not efficiently transmitted through sex (1333–1335). Studies of HCV transmission between heterosexual couples and MSM have yielded mixed results; however, studies have reported either no or minimally increased rates of HCV infection among partners of persons with HCV infection compared with partners of those without HCV (1334,1336–1338). However, data indicate that sexual transmission of HCV can occur, especially among persons with HIV infection. Increasing incidence of acute HCV infection among MSM with HIV infection has been reported in multiple U.S. (96,236,239,1339) and European cities (237,1340–1342). A recent systematic review reported an HCV incidence of 6.35 per 1,000 person years among MSM with HIV infection (1343). An association exists with high-risk and traumatic sexual practices (e.g., condomless receptive anal intercourse or receptive fisting) and concurrent genital ulcerative disease or STI-related proctitis (237,1342). HCV transmission among MSM with HIV infection has also been associated with group sex and chemsex (i.e., using recreational drugs in a sexual context) (1344–1348). Shedding of HCV in the semen and in the rectum of men with HIV infection has been documented (1349,1350). Certain studies have revealed that risk increases commensurate with increasing numbers of sex partners among heterosexual persons (1337,1338,1351–1353) and MSM with HIV infection (1349,1354–1357), especially if their partners are also coinfected with HIV (237,1340,1354–1356,1358). More recently, acute HCV infections have been reported among MSM on PrEP, increasing concerns that certain MSM might be at increased risk for incident HCV infection through condomless sexual intercourse with MSM with HCV infection (1359,1360).

Persons newly infected with HCV typically are either asymptomatic or have a mild clinical illness. HCV RNA can be detected in blood within 1–3 weeks after exposure. The average time from exposure to antibody to HCV (anti-HCV) seroconversion is 4–10 weeks, and anti-HCV can be detected among approximately 97% of persons by 6 months after exposure (1361–1364) (<https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section3>).

Chronic HCV infection develops among 75%–85% of persons with HCV infection (1365,1366), and 10%–20% of persons with chronic infection develop cirrhosis in 20–30 years of active liver disease (1367). The majority of infected persons remain unaware of their infection because they are not clinically

ill. However, infected persons are a source of transmission to others and are at risk for cirrhosis and hepatocellular carcinoma decades after infection.

HCV is primarily transmitted parenterally, usually through shared drug-injecting needles and paraphernalia. HCV also can be transmitted through exposures in health care settings as a consequence of inadequate infection control practices (1314). Transmission after receipt of blood from donors and from transplantation of tissues and organs with HCV infection has occurred only rarely since 1992, when routine screening of these donated products was mandated in the United States (1367,1369). Tattoos applied in regulated settings have not been associated with HCV transmission, although those obtained in certain settings have been linked to such transmission (1336). Occupational and perinatal exposures also can result in transmission of HCV; however, such transmission is uncommon.

Acute HCV infection is a reportable condition in 49 states. Matching viral hepatitis and HIV surveillance registries, and molecular epidemiologic assessments, can facilitate early detection of social networks of HCV transmission among MSM with HIV infection.

CDC recommends hepatitis C screening at least once in a lifetime for all adults aged ≥18 years and for all women during each pregnancy, except in settings where the prevalence of HCV infection is <0.1% (156). One-time hepatitis C testing is also recommended regardless of age, setting, or recognized conditions or exposures (e.g., HIV infection, history of injecting drug use, or children born to women with HCV infection). Routine periodic HCV testing is recommended for persons with ongoing risk factors (e.g., injecting drug use or hemodialysis).

## Diagnosis

Testing for HCV infection should include use of an FDA-cleared test for antibody to HCV (i.e., immunoassay, EIA, or enhanced CIA and, if recommended, a supplemental antibody test) followed by NAAT to detect HCV RNA for those with a positive antibody result (1370). Persons with HIV infection with low CD4<sup>+</sup> T-cell count might require further testing by NAAT because of the potential for a false-negative antibody assay.

Persons determined to have HCV infection (i.e., positive for HCV RNA) should be evaluated for treatment. Antibody to HCV remains positive after spontaneously resolving or successful treatment; therefore, subsequent testing for HCV reinfection among persons with ongoing risk factors should be limited to HCV RNA. Persons who have spontaneous resolution or who have undergone successful treatment are not immune to reinfection.

## Treatment

HCV infection is curable, and persons with diagnosed HCV infection should be linked to care and treatment. Providers should consult existing guidelines to learn about the latest advances in treating HCV infection (<https://www.hcvguidelines.org>) and with hepatitis specialists, as needed. Persons at high risk for transmitting HCV to others should be treated both for individual benefit and to prevent HCV transmission.

## Management of Sex Partners

Because incident HCV has not been demonstrated to occur among heterosexual couples followed over time (1334,1371–1373), condom use might not be necessary in such circumstances. Persons with HCV infection with one long-term, steady sex partner do not need to change their sexual practices. However, they should discuss the risk for transmission with their partner and discuss the need for testing (234) (<https://www.cdc.gov/hepatitis/hcv/index.htm>). Heterosexual persons and MSM with HCV infection and more than one partner, especially those with concurrent HIV infection, should protect their partners against HCV and HIV acquisition by using external latex condoms (237,1358,1374) and HIV PrEP. Partners of persons with HCV and HIV should be tested for both infections.

## Other Management Considerations

All persons with HCV infection for whom HIV and HBV infection status is unknown should be tested for these infections. Those who have HIV or HBV infection should be referred for or provided with recommended care and treatment. Persons without previous exposure to HAV or HBV should be vaccinated.

## Prevention

Reducing the burden of HCV infection and disease in the United States requires implementing both primary and secondary prevention activities. Primary prevention reduces or eliminates HCV transmission, whereas secondary prevention identifies persons through screening and then provides treatment to reduce chronic liver disease and other chronic diseases and HCV transmission. No vaccine for hepatitis C is available, and prophylaxis with IG is not effective in preventing HCV infection after exposure. PEP using direct-acting antivirals is not recommended.

Persons with HCV infection should be provided information about how to protect their liver from further harm (i.e., hepatotoxic agents); for instance, persons with HCV infection should be advised to avoid drinking alcohol and taking any new medicines, including over-the-counter or herbal medications, without checking with their clinician. In addition, a need for

hepatitis A and B vaccination should be determined; persons who are not immune should be vaccinated.

To reduce the risk for transmission to others, persons with HCV infection should be advised not to donate blood, body organs, other tissue, or semen; not to share any personal items that might have blood on them (e.g., toothbrushes or razors); and to cover cuts and sores on the skin to keep the virus from spreading by blood or secretions. Women with HCV infection do not need to avoid pregnancy or breastfeeding, although children born to women with HCV also should be tested for HCV.

Persons who use or inject drugs should be counseled about the importance of prevention and provided access to substance misuse treatment, including medication-assisted treatment, if indicated. Persons who inject drugs should be encouraged to take the following additional steps to reduce personal and public health risks:

- Never reuse or share syringes, water, or drug preparation equipment.
- Only use syringes obtained from a reliable source (e.g., a syringe services program or a pharmacy).
- Use a new, sterile syringe to prepare and inject drugs each time.
- If possible, use sterile water to prepare drugs; otherwise, use clean water from a reliable source (e.g., fresh tap water).
- Use a new or disinfected container (i.e., cooker) and a new filter (i.e., cotton) to prepare drugs.
- Clean the injection site with a new alcohol swab before injection.
- Safely dispose of syringes after one use.

## Postexposure Follow-Up

No PEP has been demonstrated to be effective against HCV infection. Testing for HCV is recommended for health care workers after percutaneous or perimucosal exposures to HCV-positive blood. Prompt identification of acute infection is vital because outcomes are improved when treatment is initiated early during the illness course.

## Special Considerations

### Pregnancy

All pregnant women should be screened with each pregnancy for HCV antibodies at the first prenatal visit in settings where the HCV prevalence is >0.1% (<https://www.cdc.gov/hepatitis/hcv/index.htm>) (154,155). Although the rate of transmission is highly variable, more than six of every 100 infants born to women with HCV infection become infected; this infection occurs predominantly during or near delivery, and no treatment or delivery method (e.g., cesarean delivery) has been demonstrated to decrease this risk (1375). However, the risk is increased by the presence of maternal HCV viremia

at delivery and is twofold to threefold greater if the woman has HIV infection. Although no recommendations are available for HCV treatment during pregnancy, discussion about the individual risks and benefits of postpartum treatment can be considered in accordance with existing guidance (<https://www.hcvguidelines.org/unique-populations/pregnancy>).

HCV has not been reported to be transmitted through breast milk, although mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding. Infants born to mothers with HCV infection should be tested for HCV infection; children should be tested for anti-HCV no sooner than age 18 months because anti-HCV from the mother might last until that age. If diagnosis is desired before the child reaches age 18 months, testing for HCV RNA can be performed at or after the infant's first well-child visit at age 1–2 months. HCV RNA testing can be repeated at a subsequent visit, independent of the initial HCV RNA test result (1376) (<https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section3>).

### HIV Infection

All persons with HIV infection should undergo serologic screening for HCV at initial evaluation (98) (<https://www.hcvguidelines.org>). Providers should be aware of the likelihood that MSM with HIV infection can acquire HCV after initial screening. Because acute HCV infection acquisition among persons with HIV infection can occur, especially among MSM, and regular screening of those with HIV is cost-effective (238,239,1377), periodic HCV screening should be conducted (1378–1380). For persons with HIV infection, hepatitis C screening with HCV antibody assays (followed by HCV RNA if antibody positive) can be considered at least yearly, for those at high risk for infection, and more frequently depending on specific circumstances (e.g., community HCV infection prevalence and incidence, high-risk sexual behavior, and concomitant ulcerative STIs and proctitis). Antibody to HCV remains positive after spontaneously resolved infection or successful treatment; therefore, subsequent testing for potential HCV reinfection among persons with ongoing risk should be limited to HCV RNA testing only. Indirect testing (e.g., alanine aminotransferase [ALT]) is not recommended for detecting incident HCV infections because such testing, especially if performed once a year, can miss persons who have reverted after acute HCV infection to a normal ALT level at the time of testing (239) (<https://www.hcvguidelines.org>). Conversely, ALT can be elevated by antiretroviral and other medications, alcohol, and toxins. If ALT levels are being monitored, persons with HIV infection who experience new or unexplained increases in ALT should be tested for acute

HCV infection and evaluated for possible medication toxicity or excessive alcohol use.

Continued unprotected sexual contact between partners with HIV can facilitate spread of HCV infection because the virus can be recovered from the semen of men with HIV infection (1349,1381). Specific prevention practices (e.g., barrier precautions that limit contact with body fluids during sexual contact with other MSM) should be discussed.

Because a minimal percentage of persons with HIV infection do not develop HCV antibodies, HCV RNA testing should be performed for persons with HIV infection and unexplained liver disease who are anti-HCV negative. The course of liver disease is more rapid among persons with HIV and HCV, and the risk for cirrhosis is higher than that for persons with HCV infection alone.

## Proctitis, Proctocolitis, and Enteritis

Sexually transmitted gastrointestinal syndromes include proctitis, proctocolitis, and enteritis. Evaluation for these syndromes should include recommended diagnostic procedures, including anoscopy or sigmoidoscopy, stool examination for WBCs, and microbiologic workup (e.g., gonorrhea, chlamydia [LGV PCR if available], herpes simplex NAAT, and syphilis serology). For those with enteritis, stool culture or LGV PCR also is recommended.

Proctitis is inflammation of the rectum (i.e., the distal 10–12 cm) that can be associated with anorectal pain, tenesmus, or rectal discharge. Fecal leukocytes are common. Proctitis occurs predominantly among persons who have receptive anal exposures (oral-anal, digital-anal, or genital-anal). *N. gonorrhoeae*, *C. trachomatis* (including LGV serovars), HSV, and *T. pallidum* are the most common STI pathogens. Genital HSV and LGV proctitis are more prevalent among persons with HIV infection (545,556,1382). *M. genitalium* has been detected in certain cases of proctitis and might be more common among persons with HIV infection (937,1382). *N. meningitidis* has been identified as an etiology of proctitis among MSM with HIV infection (1383).

Proctocolitis is associated with symptoms of proctitis, diarrhea or abdominal cramps, and inflammation of the colonic mucosa extending to 12 cm above the anus. Fecal leukocytes might be detected on stool examination, depending on the pathogen. Proctocolitis can be acquired through receptive anal intercourse or by oral-anal contact, depending on the pathogen.

Pathogenic organisms include *Campylobacter* species, *Shigella* species, *E. histolytica*, LGV serovars of *C. trachomatis*, and *T. pallidum*. Among immunosuppressed persons with HIV infection, CMV or other opportunistic agents should be considered. The clinical presentation can be mistaken for

inflammatory bowel disease or malignancy, resulting in a delayed diagnosis (1384,1385).

Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis. Fecal leukocytes might be detected on stool examination, depending on the pathogen. When outbreaks of gastrointestinal illness occur among social or sexual networks of MSM, clinicians should consider sexual transmission as a mode of spread and provide counseling accordingly. Sexual practices that can facilitate transmission of enteric pathogens include oral-anal contact or, in certain instances, direct genital-anal contact. *G. lamblia* is the most frequently implicated parasite, and bacterial pathogens include *Shigella* species, *Salmonella*, *E. coli*, *Campylobacter* species, and *Cryptosporidium*. Outbreaks of *Shigella* species, *Campylobacter*, *Cryptosporidium*, and microsporidiosis have been reported among MSM (259,274,1386,1387). Multiple enteric pathogens and concurrent STIs have also been reported. Among immunosuppressed persons with HIV infection, CMV or other opportunistic pathogens should be considered.

## Diagnostic and Treatment Considerations for Acute Proctitis

### Diagnosis

Persons with symptoms of acute proctitis should be examined by anoscopy. A Gram-stained smear of any anorectal exudate from anoscopy or anal examination should be examined for polymorphonuclear leukocytes. All persons should be evaluated for herpes simplex (preferably by NAAT of rectal lesions), *N. gonorrhoeae* (NAAT or culture), *C. trachomatis* (NAAT), and *T. pallidum* (darkfield of lesion if available and serologic testing). If the *C. trachomatis* NAAT test is positive on a rectal swab and severe symptoms associated with LGV are present (including rectal ulcers, anal discharge, bleeding, ≥10 WBCs on Gram stain, and tenesmus), patients should be treated empirically for LGV. Molecular testing for LGV is not widely available or not FDA cleared, and results are not typically available in time for clinical decision-making. However, if available, molecular PCR testing for *C. trachomatis* serovars L1, L2, or L3 can be considered for confirming LGV (553).

The pathogenic role of *M. genitalium* in proctitis is unclear. For persons with persistent symptoms after standard treatment, providers should consider testing for *M. genitalium* with NAAT and treat if positive (see *Mycoplasma genitalium*).

### Treatment

Acute proctitis among persons who have anal exposure through oral, genital, or digital contact is usually sexually acquired (1382,1388). Presumptive therapy should be

initiated while awaiting results of laboratory tests for persons with anorectal exudate detected on examination or polymorphonuclear leukocytes detected on a Gram-stained smear of anorectal exudate or secretions. Such therapy also should be initiated when anoscopy or Gram stain is not available and the clinical presentation is consistent with acute proctitis for persons reporting receptive anal exposures.

#### Recommended Regimen for Acute Proctitis

Ceftriaxone 500 mg\* IM in a single dose  
plus  
Doxycycline 100 mg orally 2 times/day for 7 days<sup>†</sup>

\* For persons weighing  $\geq 150$  kg, 1 g of ceftriaxone should be administered.

<sup>†</sup> Doxycycline course should be extended to 100 mg orally 2 times/day for 21 days in the presence of bloody discharge, perianal or mucosal ulcers, or tenesmus and a positive rectal chlamydia test.

Bloody discharge, perianal ulcers, or mucosal ulcers among persons with acute proctitis and rectal chlamydia (NAAT) should receive presumptive treatment for LGV with an extended course of doxycycline 100 mg orally 2 times/day for 3 weeks (1389,1390) (see Lymphogranuloma Venereum). If painful perianal ulcers are present or mucosal ulcers are detected on anoscopy, presumptive therapy should also include a regimen for genital herpes (see Genital Herpes).

### Diagnostic and Treatment Considerations for Proctocolitis or Enteritis

Treatment for proctocolitis or enteritis should be directed to the specific enteric pathogen identified. Multiple stool examinations might be necessary for detecting *Giardia*, and special stool preparations are required for diagnosing cryptosporidiosis and microsporidiosis. Diagnostic and treatment recommendations for all enteric infections are beyond the scope of these guidelines. Providers should be aware of the potential for antimicrobial-resistant pathogens, particularly during outbreaks of *Shigella* and *Campylobacter* among sexual networks of MSM where increased resistance to azithromycin, fluoroquinolones, and isolates resistant to multiple antibiotics have been described (266,272,273,1391,1392).

### Other Management Considerations

To minimize transmission and reinfection, patients treated for acute proctitis should be instructed to abstain from sexual intercourse until they and their partners have been treated (i.e., until completion of a 7-day regimen and symptoms have resolved). Studies have reported that behaviors that facilitate enteric pathogen transmission might be associated with acquisition of other STIs, including HIV infection. All persons with acute proctitis and concern for sexually

transmitted proctocolitis or enteritis should be tested for HIV, syphilis, gonorrhea, and chlamydia (at other exposed sites). PEP should be considered for exposures that present a risk for HIV acquisition. For ongoing risk for HIV acquisition, PrEP should be considered.

Evidence-based interventions for preventing acquisition of sexually transmitted enteric pathogens are not available. However, extrapolating from general infection control practices for communicable diseases and established STI prevention practices, recommendations include avoiding contact with feces during sex, using barriers, and washing hands after handling materials that have been in contact with the anal area (i.e., barriers and sex toys) and after touching the anus or rectal area.

### Follow-Up

Follow-up should be based on specific etiology and severity of clinical symptoms. For proctitis associated with gonorrhea or chlamydia, retesting for the respective pathogen should be performed 3 months after treatment.

### Management of Sex Partners

Partners who have had sexual contact with persons treated for gonorrhea or chlamydia <60 days before the onset of the persons symptoms should be evaluated, tested, and presumptively treated for the respective infection. Partners of persons with proctitis should be evaluated for any diseases diagnosed in the index partner. Sex partners should abstain from sexual contact until they and their partners are treated. No specific recommendations are available for screening or treating sex partners of persons with diagnosed sexually transmitted enteric pathogens; however, partners should seek care if symptomatic.

### Special Considerations

#### Drug Allergy, Intolerance, and Adverse Reactions

Allergic reactions with third-generation cephalosporins (e.g., ceftriaxone) are uncommon among persons with a history of penicillin allergy (620,631,658,896).

#### HIV Infection

Persons with HIV infection and acute proctitis might present with bloody discharge, painful perianal ulcers, or mucosal ulcers and LGV and herpes proctitis are more prevalent among this population. Presumptive treatment in such cases should include a regimen for genital herpes and LGV.

## Ectoparasitic Infections

### Pediculosis Pubis

Persons who have pediculosis pubis (i.e., pubic lice) usually seek medical attention because of pruritus or because they notice lice or nits on their pubic hair. Pediculosis pubis is caused by the parasite *Phthirus pubis* and is usually transmitted by sexual contact (1393).

### Diagnosis

The clinical diagnosis is based on typical symptoms of itching in the pubic region. Lice and nits can be observed on pubic hair.

### Treatment

#### Recommended Regimens for Pediculosis Pubis

**Permethrin 1% cream rinse** applied to affected areas and washed off after 10 minutes

or

**Pyrethrin with piperonyl butoxide** applied to the affected area and washed off after 10 minutes

#### Alternative Regimens

**Malathion 0.5% lotion** applied to affected areas and washed off after 8–12 hours

or

**Ivermectin 250 µg/kg body weight orally, repeated in 7–14 days**

Reported resistance to pediculicides (permethrin and pyrethrin) has been increasing and is widespread (1394,1395). Malathion can be used when treatment failure is believed to have occurred as a result of resistance. The odor and longer duration of application associated with malathion therapy make it a less attractive alternative compared with the recommended pediculicides. Ivermectin has limited ovicidal activity (1396). Ivermectin might not prevent recurrences from eggs at the time of treatment, and therefore treatment should be repeated in 7–14 days (1397,1398). Ivermectin should be taken with food because bioavailability is increased, thus increasing penetration of the drug into the epidermis. Adjustment of ivermectin dosage is not required for persons with renal impairment; however, the safety of multiple doses among persons with severe liver disease is unknown. Lindane is not recommended for treatment of pediculosis because of toxicity, contraindications for certain populations (pregnant and breastfeeding women, children aged <10 years, and those with extensive dermatitis), and complexity of administration.

### Other Management Considerations

The recommended regimens should not be applied to the eyes. Pediculosis of the eyelashes should be treated by applying occlusive ophthalmic ointment or petroleum jelly to the eyelid

margins 2 times/day for 10 days. Bedding and clothing should be decontaminated (i.e., machine washed and dried by using the heat cycle or dry cleaned) or removed from body contact for at least 72 hours. Fumigation of living areas is unnecessary. Pubic hair removal has been associated with atypical patterns of pubic lice infestation and decreasing incidence of infection (537,1399). Persons with pediculosis pubis should be evaluated for HIV, syphilis, chlamydia, and gonorrhea.

### Follow-Up

Evaluation should be performed after 1 week if symptoms persist. Retreatment might be necessary if lice are found or if eggs are observed at the hair-skin junction. If no clinical response is achieved to one of the recommended regimens, retreatment with an alternative regimen is recommended.

### Management of Sex Partners

Sex partners within the previous month should be treated. Sexual contact should be avoided until patients and partners have been treated, bedding and clothing decontaminated, and reevaluation performed to rule out persistent infection.

### Special Considerations

#### Pregnancy

Existing data from human participants demonstrate that pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Because no teratogenicity or toxicity attributable to ivermectin has been observed during human pregnancy experience, ivermectin is classified as “human data suggest low risk” during pregnancy and probably compatible with breastfeeding (431).

#### HIV Infection

Persons who have pediculosis pubis and HIV infection should receive the same treatment regimen as those who do not have HIV.

## Scabies

Scabies is a skin infestation caused by the mite *Sarcoptes scabiei*, which causes pruritus. Sensitization to *S. scabiei* occurs before pruritus begins. The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfection. Scabies among adults frequently is sexually acquired, although scabies among children usually is not (1400–1402).

### Diagnosis

Scabies diagnosis is made by identifying burrows, mites, eggs, or the mites’ feces from affected areas. Skin scrapings can be examined under the microscope to identify organisms, although

this method has low sensitivity and is time consuming (1403). Alternatively, noninvasive examination of the affected skin by using videodermatoscopy, videomicroscopy, or dermoscopy can be used, each of which has high sensitivity and specificity, particularly when performed by experienced operators (1404). Low-technology strategies include the burrow ink test and the adhesive tape test.

## Treatment

### Recommended Regimens for Scabies

**Permethrin 5% cream** applied to all areas of the body from the neck down and washed off after 8–14 hours

or

**Ivermectin 200 ug/kg** body weight orally, repeated in 14 days\*

or

**Ivermectin 1% lotion** applied to all areas of the body from the neck down and washed off after 8–14 hours; repeat treatment in 1 week if symptoms persist

\* Oral ivermectin has limited ovicidal activity; a second dose is required for eradication.

### Alternative Regimen

**Lindane 1%** 1 oz of lotion or 30 g of cream applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours\*

\* Infants and children aged <10 years should not be treated with lindane.

Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies (1405–1410). Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin (e.g., azithromycin, trimethoprim/sulfamethoxazole [Bactrim], or cetirizine [Zyrtec]), and cost. Permethrin is safe and effective with a single application (1411). Ivermectin has limited ovicidal activity and might not prevent recurrences of eggs at the time of treatment; therefore, a second dose of ivermectin should be administered 14 days after the first dose (1412). Ivermectin should be taken with food because bioavailability is increased, thereby increasing penetration of the drug into the epidermis. Adjustments to ivermectin dosing are not required for patients with renal impairment; however, the safety of multiple doses among patients with severe liver disease is unknown.

Lindane is an alternative regimen because it can cause toxicity (1413); it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed (1414–1416). Lindane is not recommended for pregnant and breastfeeding women, children aged <10 years, and persons with extensive dermatitis. Seizures have occurred when lindane was applied after a bath or used by patients who had extensive dermatitis. Aplastic anemia after lindane use also has been reported (1413). Lindane resistance has been reported in some areas of the world, including parts of the United States (1413).

## Other Management Considerations

Bedding and clothing should be decontaminated (i.e., either machine washed and dried by using the heat cycle or dry cleaned) or removed from body contact for >72 hours. Fumigation of living areas is unnecessary. Persons with scabies should be advised to keep fingernails closely trimmed to reduce injury from excessive scratching (1417).

### Crusted Scabies

Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. Crusted scabies is transmitted more easily than scabies (1418). No controlled therapeutic studies for crusted scabies have been conducted, and a recommended treatment remains unclear. Substantial treatment failure might occur with a single-dose topical scabicide or with oral ivermectin treatment. Combination treatment is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 ug/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases (1419). Lindane should be avoided because of the risks for neurotoxicity with heavy applications on denuded skin.

### Follow-Up

The rash and pruritus of scabies might persist for <2 weeks after treatment. Symptoms or signs persisting for >2 weeks can be attributed to multiple factors. Treatment failure can occur as a result of resistance to medication or faulty application of topical scabicides. These medications do not easily penetrate into thick, scaly skin of persons with crusted scabies, perpetuating the harboring of mites in these difficult-to-penetrate layers. In the absence of recommended contact treatment and decontamination of bedding and clothing, persisting symptoms can be attributed to reinfection by family members or fomites. Finally, other household mites can cause symptoms to persist as a result of cross-reactivity between antigens. Even when treatment is successful, reinfection is avoided, and cross-reactivity does not occur, symptoms can persist or worsen as a result of allergic dermatitis.

Retreatment 2 weeks after the initial treatment regimen can be considered for those persons who are still symptomatic or when live mites are observed. Use of an alternative regimen is recommended for those persons who do not respond initially to the recommended treatment.

## Management of Sex Partners and Household Contacts

Persons who have had sexual, close personal, or household contact with the patient within the month preceding scabies infestation should be examined. Those identified as being infested should be provided treatment.

## Management of Outbreaks in Communities, Nursing Homes, and Other Institutional Settings

Scabies epidemics frequently occur in nursing homes, hospitals, residential facilities, and other communities (1420,1421). Control of an epidemic can only be achieved by treating the entire population at risk. Ivermectin can be considered in these settings, especially if treatment with topical scabicides fails. Mass treatment with oral ivermectin is highly effective in decreasing prevalence in settings where scabies is endemic (1422). Epidemics should be managed in consultation with a specialist.

## Special Considerations

### Infants, Young Children, and Pregnant or Lactating Women

Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. Infants and children aged <10 years should not be treated with lindane. Ivermectin likely poses a low risk to pregnant women and is likely compatible with breastfeeding; however, because of limited data regarding ivermectin use for pregnant and lactating women, permethrin is the preferred treatment (431) (see Pediculosis Pubis).

### HIV Infection

Persons with HIV infection who have uncomplicated scabies should receive the same treatment regimens as those who do not have HIV. Persons with HIV infection and others who are immunosuppressed are at increased risk for crusted scabies and should be managed in consultation with a specialist.

## Sexual Assault and Abuse and STIs

### Adolescents and Adults

These guidelines are primarily limited to the identification, prophylaxis, and treatment of STIs and conditions among adolescent and adult female sexual assault survivors. However, some of the following guidelines might still apply to male sexual assault survivors. Documentation of findings, collection of nonmicrobiologic specimens for forensic purposes, and management of potential pregnancy or physical and

psychological trauma are beyond the scope of these guidelines. Examinations of survivors of sexual assault should be conducted by an experienced clinician in a way that minimizes further trauma to the person. The decision to obtain genital or other specimens for STI diagnosis should be made on an individual basis. Care systems for survivors should be designed to ensure continuity, including timely review of test results, support adherence, and monitoring for adverse reactions to any prescribed therapeutic or prophylactic regimens. Laws in all 50 states limit the evidentiary use of a survivor's previous sexual history, including evidence of previously acquired STIs, as part of an effort to undermine the credibility of the survivor's testimony. Evidentiary privilege against revealing any aspect of the examination or treatment also is enforced in most states. Although it rarely occurs, STI diagnoses might later be accessed, and the survivor and clinician might opt to defer testing for this reason. Although collection of specimens at initial examination for laboratory STI diagnosis gives the survivor and clinician the option of deferring empiric prophylactic antimicrobial treatment, compliance with follow-up visits is typically poor (1423–1425). Among sexually active adults, identification of an STI might represent an infection acquired before the assault, and therefore might be more important for the medical management of the patient than for legal purposes.

Trichomoniasis, BV, gonorrhea, and chlamydia are the most frequently diagnosed infections among women who have been sexually assaulted. Such conditions are prevalent among the population, and detection of these infections after an assault does not necessarily imply acquisition during the assault. However, a postassault examination presents an important opportunity for identifying or preventing an STI. Chlamydial and gonococcal infections among women are of particular concern because of the possibility of ascending infection. In addition, HBV infection can be prevented through postexposure vaccination (see Hepatitis B Virus Infection). Because persons who have been sexually assaulted also are at risk for acquiring HPV infection, and the efficacy of the HPV vaccine is high (1426,1427), HPV vaccination is also recommended for females and males through age 26 years (<https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html>) (11). Reproductive-aged female survivors should be evaluated for pregnancy and offered emergency contraception.

### Evaluating Adolescents and Adults for STIs

#### Initial Examination

Decisions to perform the following tests should be made on an individual basis. An initial examination after a sexual assault might include the following:

- NAATs for *C. trachomatis* and *N. gonorrhoeae* at the sites of penetration or attempted penetration should be performed (553). These tests are preferred for diagnostic evaluation of adolescent or adult sexual assault survivors.
- Females should be offered NAAT testing for *T. vaginalis* from a urine or vaginal specimen. POC or wet mount with measurement of vaginal pH and KOH application for the whiff test from vaginal secretions should be performed for evidence of BV and candidiasis, especially if vaginal discharge, malodor, or itching is present.
- MSM should be offered screening for *C. trachomatis* and *N. gonorrhoeae* if they report receptive oral or anal sex during the preceding year, regardless of whether sexual contact occurred at these anatomic sites during the assault. Anoscopy should be considered in instances of reported anal penetration.
- A serum sample should be performed for HIV, HBV, and syphilis infection.

## Treatment

Compliance with follow-up visits is poor among survivors of sexual assault (1423–1425). Consequently, the following routine presumptive treatments after a sexual assault are recommended:

- An empiric antimicrobial regimen for chlamydia, gonorrhea, and trichomonas for women and chlamydia and gonorrhea for men.
- Emergency contraception should be considered when the assault could result in pregnancy (see Emergency Contraception).
- Postexposure hepatitis B vaccination (without HBIG) if the hepatitis status of the assailant is unknown and the survivor has not been previously vaccinated. If the assailant is known to be HBsAg positive, unvaccinated survivors should receive both hepatitis B vaccine and HBIG. The vaccine and HBIG, if indicated, should be administered to sexual assault survivors at the time of the initial examination, and follow-up doses of vaccine should be administered 1–2 and 4–6 months after the first dose. Survivors who were previously vaccinated but did not receive postvaccination testing should receive a single vaccine booster dose (see Hepatitis B Virus Infection).
- HPV vaccination for female and male survivors aged 9–26 years who have not been vaccinated or are incompletely vaccinated (11) (<https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html>). The vaccine should be administered to sexual assault survivors at the time of the initial examination, and follow-up doses should be administered at 1–2 months and 6 months after the first dose. A 2-dose schedule (0 and 6–12 months) is

recommended for persons initiating vaccination before age 15 years.

- Recommendations for HIV PEP are made on a case-by-case basis according to risk (see Risk for Acquiring HIV Infection; Recommendations for Postexposure HIV Risk Assessment of Adolescents and Adults <72 Hours After Sexual Assault).

### Recommended Regimen for Adolescent and Adult Female Sexual Assault Survivors

Ceftriaxone 500 mg* IM in a single dose plus
Doxycycline 100 mg 2 times/day orally for 7 days plus
Metronidazole 500 mg 2 times/day orally for 7 days

\* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

### Recommended Regimen for Adolescent and Adult Male Sexual Assault Survivors

Ceftriaxone 500 mg* IM in a single dose plus
Doxycycline 100 mg 2 times/day orally for 7 days

\* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

Clinicians should counsel persons regarding the possible benefits and toxicities associated with these treatment regimens; gastrointestinal side effects can occur with this combination. The efficacy of these regimens in preventing infections after sexual assault has not been evaluated. For those requiring alternative treatments, refer to the specific sections in this report relevant to the specific organisms.

## Other Management Considerations

At the initial examination and, if indicated, at follow-up examinations, patients should be counseled regarding symptoms of STIs and the need for immediate examination if symptoms occur. Further, they should be instructed to abstain from sexual intercourse until STI prophylactic treatment is completed.

## Follow-Up

After the initial postassault examination, follow-up examinations provide an opportunity to detect new infections acquired during or after the assault, complete hepatitis B and HPV vaccinations, if indicated, complete counseling and treatment for other STIs, and monitor side effects and adherence to PEP, if prescribed. If initial testing was performed, follow-up evaluation should be conducted in <1 week to ensure that results of positive tests can be discussed promptly with the survivor, treatment is provided if not administered at the initial visit, and any follow-up for infections can be arranged. If initial tests are negative and treatment was not provided,

examination for STIs can be repeated 1–2 weeks after the assault; repeat testing detects infectious organisms that might not have reached sufficient concentrations to produce positive test results at the time of initial examination. For survivors who are treated during the initial visit, regardless of whether testing was performed, posttreatment testing should be conducted only if the person reports having symptoms. If initial test results were negative and infection in the assailant cannot be ruled out, serologic tests for syphilis can be repeated at 4–6 weeks and 3 months; HIV testing can be repeated at 6 weeks and at 3 months by using methods to identify acute HIV infection.

### Risk for Acquiring HIV Infection

HIV seroconversion has occurred among persons whose only known risk factor was sexual assault or sexual abuse; however, the frequency of this occurrence likely is low (1428,1429). In consensual sex, the per-act risk for HIV transmission from vaginal intercourse is 0.08%, and for receptive anal intercourse, 1.38% (192). The per-act risk for HIV transmission from oral sex is substantially lower. Specific circumstances of an assault (e.g., bleeding, which often accompanies trauma) might increase risk for HIV transmission in cases involving vaginal, anal, or oral penetration. Site of exposure to ejaculate, viral load in ejaculate, and the presence of an STI or genital lesions in the assailant or survivor also might increase risk for HIV acquisition.

PEP with a 28-day course of zidovudine was associated with an 81% reduction in risk for acquiring HIV in a study of health care workers who had percutaneous exposures to HIV-infected blood (1430). On the basis of these results and results from animal studies, PEP has been recommended for health care workers who have occupational exposures to HIV (1431). These findings have been extrapolated to nonoccupational injecting drug and sexual HIV exposures, including sexual assault. The possibility of HIV exposure from the assault should be assessed at the initial examination; survivors determined to be at risk for acquiring HIV should be informed about the possible benefit of PEP in preventing HIV infection. Initiation of PEP as soon as possible after the exposure increases the likelihood of prophylactic benefit.

Multiple factors affect the medical recommendation for PEP and affect the assault survivor's acceptance of that recommendation. These factors include the likelihood of the assailant having HIV, any exposure characteristics that might increase the risk for HIV transmission, the time elapsed after the event, and the potential benefits and risks associated with PEP (1431). Determination of the assailant's HIV status at the time of the postassault examination is usually not possible. Therefore, health care providers should assess any available information concerning the characteristics and

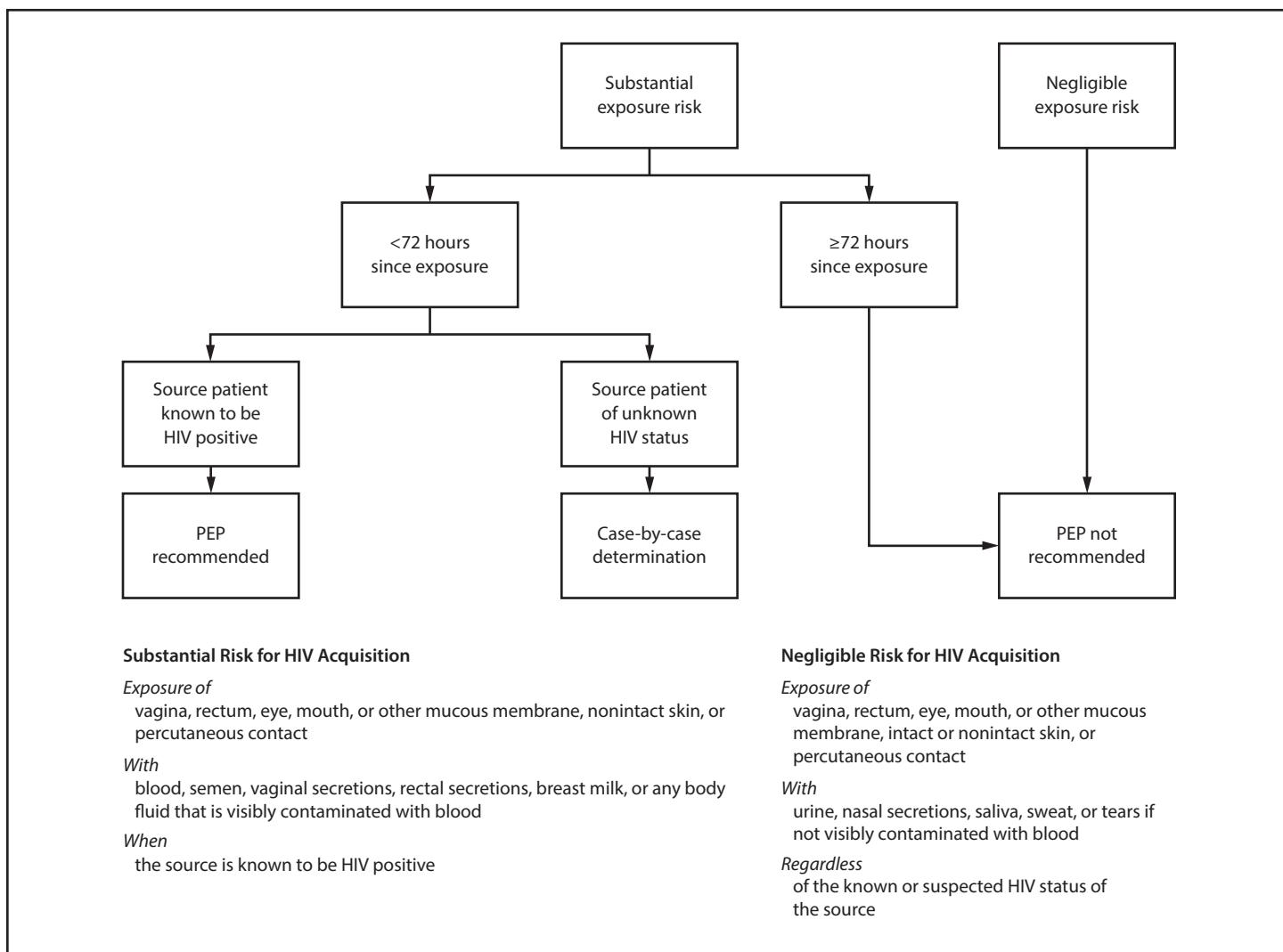
HIV risk behaviors of the assailant (e.g., being an MSM or using injecting drugs), local epidemiology of HIV/AIDS, and exposure characteristics of the assault. When an assailant's HIV status is unknown, determinations about risk for HIV transmission to the survivor should be based on whether vaginal or anal penetration occurred; whether ejaculation occurred on mucous membranes; whether multiple assailants were involved; whether mucosal lesions were present in the assailant or survivor; and any other characteristics of the assault, survivor, or assailant that might increase risk for HIV transmission.

If PEP is offered, the following information should be discussed with the survivor: the necessity of early initiation of PEP to optimize potential benefits (i.e., as soon as possible after and <72 hours after the assault), the importance of close follow-up, the benefit of adherence to recommended dosing, and potential adverse effects of antiretroviral medications. Providers should emphasize that severe adverse effects are rare from PEP (1431–1435). Clinical management of the survivor should be implemented according to the HIV PEP guidelines and in collaboration with specialists (1436). Health care providers should provide an initial course of 3–7 days of medication (i.e., a starter pack) with a prescription for the remainder of the course, or, if starter packs are unavailable, they should provide a prescription for an entire 28-day course. Provision of the entire 28-day PEP medication supply at the initial visit has been reported to increase likelihood of adherence, especially when patients have difficulty returning for multiple follow-up visits (1437). Routinely providing starter packs or the entire 28-day course requires that health care providers stock PEP drugs in their practice setting or have an established agreement with a pharmacy to stock, package, and urgently dispense PEP drugs with required administration instructions. Uninsured patients or those with high copayments can be enrolled in a patient-assistance program to ensure access to PEP medications. An early follow-up visit should be scheduled at which health care providers can discuss the results of HIV and STI testing, provide additional counseling and support, provide indicated vaccines not administered at the initial evaluation, assess medication side effects and adherence, or provide an altered PEP medication regimen if indicated by side effects or laboratory test results.

### Recommendations for Postexposure HIV Risk Assessment of Adolescents and Adults <72 Hours After Sexual Assault

Health care providers should do the following:

- Assess risk for HIV infection in the assailant, and test that person for HIV whenever possible.
- Use the algorithm to evaluate the survivor for the need for HIV PEP (Figure) (1436).

**FIGURE.** Algorithm to evaluate the need for nonoccupational HIV postexposure prophylaxis among adult and adolescent survivors of sexual assault

**Source:** Adapted from Announcement: updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:458.

**Abbreviation:** PEP = postexposure prophylaxis.

- Consult with a specialist in HIV treatment if PEP is being considered.
- If the survivor appears to be at risk for acquiring HIV from the assault, discuss PEP, including benefits and risks.
- If the survivor chooses to start PEP, provide an initial course of 3–7 days of medication (i.e., a starter pack) with a prescription for the remainder of the course or provide a prescription for an entire 28-day course. Schedule an early follow-up visit to discuss test results and provide additional counseling (1438).
- If PEP is started, obtain serum creatinine, AST, and alanine aminotransferase at baseline.
- Perform an HIV antibody test at original assessment; repeat at 6 weeks and 3 months.

- Counsel the survivor regarding ongoing risk for HIV acquisition and about HIV PrEP, and provide referrals to a PrEP provider.

Assistance with PEP-related decisions can be obtained by calling the National Clinician's Post Exposure Prophylaxis Hotline (PEP Line) (telephone: 888-448-4911).

## Sexual Assault or Abuse of Children

These guidelines are limited to the identification and treatment of STIs in prepubertal children. Management of the psychosocial or legal aspects of the sexual assault or abuse of children is beyond the scope of these guidelines.

Identification of STIs in children past the neonatal period strongly indicates sexual abuse (1438). The importance of

identifying a sexually transmitted organism for such children as evidence of possible child sexual abuse varies by pathogen. Postnatally acquired gonorrhea, syphilis, chlamydia, and *T. vaginalis* infection and nontransfusion, nonperinatally acquired HIV infection are indicative of sexual abuse. Sexual abuse should be suspected when anogenital herpes or anogenital warts are diagnosed. Investigation of sexual abuse among children who have an infection that might have been transmitted sexually should be conducted in compliance with recommendations by clinicians who have experience and training in all elements of the evaluation of child abuse, neglect, and assault. The social significance of an infection that might have been acquired sexually varies by the specific organism, as does the threshold for reporting suspected child sexual abuse (Table 8). When any STI has been diagnosed in a child, efforts should be made in consultation with a specialist to evaluate the possibility of sexual abuse, including conducting a history and physical examination for evidence of abuse and diagnostic testing for other commonly occurring STIs (1439–1441).

The general rule that STIs beyond the neonatal period are evidence of sexual abuse has exceptions. For example, genital infection with *T. vaginalis* (1442) or rectal or genital infection with *C. trachomatis* among young children might be the result of perinatally acquired infection and has, in certain cases of chlamydial infection, persisted for as long as 2–3 years (1443–1445), although perinatal chlamydial infection is now uncommon because of prenatal screening and treatment of pregnant women. Genital warts have been diagnosed among children who have been sexually abused (1426) but also among children who have no other evidence of sexual abuse (1446,1447); lesions appearing for the first time in a child aged >5 years are more likely to have been caused by sexual transmission (1448). BV has been diagnosed among children

who have been abused but its presence alone does not prove sexual abuse. The majority of HBV infections among children result from household exposure to persons who have chronic HBV infection rather than sexual abuse.

## Reporting

All U.S. states and territories have laws that require reporting of child abuse. Although the exact requirements differ by state or territory, if a health care provider has reasonable cause to suspect child abuse, a report must be made (1448). Health care providers should contact their state or local child protection service agency regarding child abuse reporting requirements.

## Evaluating Children for STIs

Evaluating children for sexual assault or abuse should be conducted in a manner designed to minimize pain and trauma to the child. Examinations and collection of vaginal specimens in prepubertal girls can be extremely uncomfortable and should be performed by an experienced clinician to avoid psychological and physical trauma to the child. The decision to obtain genital or other specimens from a child to evaluate for STIs should be made on an individual basis. However, children who received a diagnosis of one STI should be screened for other STIs. History and reported type of sexual contact might not be a reliable indicator, and urogenital, pharyngeal, and rectal testing should be considered for preverbal children and children who cannot verbalize details of the assault (1438,1449). Factors that should lead the physician to consider testing for STIs include the following (1449):

- The child has experienced penetration or has evidence of recent or healed penetrative injury to the genitals, anus, or oropharynx.
- The child has been abused by a stranger.

**TABLE 8. Implications of commonly encountered sexually transmitted or sexually associated infections for diagnosis and reporting of sexual abuse among infants and prepubertal children**

Infection	Evidence for sexual abuse	Recommended action
Gonorrhea*	Diagnostic	Report <sup>†</sup>
Syphilis*	Diagnostic	Report <sup>†</sup>
HIV <sup>§</sup>	Diagnostic	Report <sup>†</sup>
<i>Chlamydia trachomatis</i> *	Diagnostic	Report <sup>†</sup>
<i>Trichomonas vaginalis</i> *	Diagnostic	Report <sup>†</sup>
Anogenital herpes	Suspicious	Consider report <sup>†,¶</sup>
Condylomata acuminata (anogenital warts)*	Suspicious	Consider report <sup>†,¶,**</sup>
Anogenital molluscum contagiosum	Inconclusive	Medical follow-up
Bacterial vaginosis	Inconclusive	Medical follow-up

**Sources:** Adapted from Kellogg N; American Academy of Pediatrics Committee on Child Abuse and Neglect. The evaluation of child abuse in children. Pediatrics 2005;16:506–12; Adams JA, Farst KJ, Kellogg ND. Interpretation of medical findings in suspected child abuse: an update for 2018. J Pediatr Adolesc Gynecol 2018;31:225–31.

\* If unlikely to have been perinatally acquired and vertical transmission, which is rare, is excluded.

† Reports should be made to the local or state agency mandated to receive reports of suspected child abuse or neglect.

§ If unlikely to have been acquired perinatally or through transfusion.

¶ Unless a clear history of autoinoculation exists.

\*\* Report if evidence exists to suspect abuse, including history, physical examination, or other identified infections. Lesions appearing for the first time in a child aged >5 years are more likely to have been caused by sexual transmission.

- The child has been abused by an assailant known to be infected with an STI or at high risk for STIs (e.g., injecting drug user, MSM, person with multiple sex partners, or person with a history of STIs).
- The child has a sibling, other relative, or another person in the household with an STI.
- The child lives in an area with a high rate of STIs in the community.
- The child has signs or symptoms of STIs (e.g., vaginal discharge or pain, genital itching or odor, urinary symptoms, or genital lesions or ulcers).
- The child or parent requests STI testing.
- The child is unable to verbalize details of the assault.

If a child has symptoms, signs, or evidence of an infection that might be sexually transmitted, the child should be tested for common STIs before initiation of any treatment that might interfere with diagnosing other STIs. Because of the legal and psychosocial consequences of a false-positive diagnosis, only tests with high specificities should be used. The potential benefit to the child of a reliable STI diagnosis justifies deferring presumptive treatment until specimens for highly specific tests are obtained by providers with experience in evaluating sexually abused and assaulted children.

Evaluations should be performed on a case-by-case basis, according to history of assault or abuse and in a manner that minimizes the possibility for psychological trauma and social stigma. If the initial exposure was recent, the infectious organisms acquired through the exposure might not have produced sufficient concentrations to result in positive test results or examination findings (1450). Alternatively, positive test results after a recent exposure might represent the assailant's secretions (but would nonetheless be an indication for treatment of the child). A second visit approximately 2–6 weeks after the most recent sexual exposure should be scheduled to include a repeat physical examination and collection of additional specimens to identify any infection that might not have been detected at the time of initial evaluation. A single evaluation might be sufficient if the child was abused for an extended period and if a substantial amount of time elapsed between the last suspected episode of abuse and the medical evaluation. Compliance with follow-up appointments might be improved when law enforcement personnel or child protective services are involved.

## Initial Examination

Visual inspection of the genital, perianal, and oral areas for genital discharge, odor, bleeding, irritation, warts, and ulcerative lesions should be performed during initial examination. The clinical manifestations of certain STIs are different for children than for adults. For example, typical

vesicular lesions might be absent even in the presence of HSV infection. The following should be performed during the initial examination, if STI testing is indicated:

- Testing for *N. gonorrhoeae* and *C. trachomatis* can be performed from specimens collected from the pharynx and rectum, as well as the vagina for girls and urine for boys. Cervical specimens are not recommended for prepubertal girls. For boys with a urethral discharge, a meatal specimen discharge is an adequate substitute for an intraurethral swab specimen. Culture or NAAT can be used to test for *N. gonorrhoeae* and *C. trachomatis*. Although data regarding NAAT for children are more limited and performance is test dependent (553), no evidence demonstrates that performance of NAAT for detection of *N. gonorrhoeae* or *C. trachomatis* among children differs from that among adults. Only FDA-cleared NAAT assays should be used. Consultation with an expert is necessary before using NAAT in this context, both to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals (e.g., *N. meningitidis*, *N. sicca*, *N. lactamica*, *N. cinerea*, or *M. catarrhalis*) and to ensure correct interpretation of results. Because of the implications of a diagnosis of *N. gonorrhoeae* or *C. trachomatis* infection in a child, only CLIA-validated, FDA-cleared NAATs should be used (837). If culture for the isolation of *N. gonorrhoeae* or *C. trachomatis* is performed, only standard culture procedures should be followed. Specimens from the vagina, urethra, pharynx, or rectum should be streaked onto selective media for isolation of *N. gonorrhoeae*, and all presumptive isolates of *N. gonorrhoeae* should be identified definitively by at least two tests that involve different approaches (e.g., biochemical, enzyme substrate, or molecular probes). Gram stains are inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. Specimens (either NAAT or culture, including any isolates) obtained before treatment should be preserved for further validation if needed. When a specimen is positive, the result should be confirmed either by retesting the original specimen or obtaining another. Because of the overall low prevalence of *N. gonorrhoeae* and *C. trachomatis* among children, false-positive results can occur, and all specimens that are initially positive should be confirmed.

- Testing for *T. vaginalis* should not be limited to girls with vaginal discharge if other indications for vaginal testing exist because evidence indicates that asymptomatic sexually abused children might be infected with *T. vaginalis* and might benefit from treatment (1451,1452). NAAT can be used as an alternative or in addition to culture and wet

mount, especially in settings where culture and wet mount of vaginal swab specimens are not obtainable. Data regarding use of NAATs for detection of *T. vaginalis* among children are limited; however, no evidence indicates that performance of NAAT for detection of *T. vaginalis* for children would differ from that for adults. Consultation with an expert is necessary before using NAAT in this context to ensure correct interpretation of results. Because of the implications of a diagnosis of *T. vaginalis* infection in a child, only CLIA-validated, FDA-cleared NAATs should be used (837). POC tests for *T. vaginalis* have not been validated for prepubertal children and should not be used. In the case of a positive specimen, the result should be confirmed either by retesting the original specimen or obtaining another. Because of the overall low prevalence of *T. vaginalis* among children, false-positive results can occur, and all specimens that are initially positive should be confirmed.

- HSV can be indicative of sexual abuse; therefore, specimens should be obtained from all vesicular or ulcerative genital or perianal lesions and sent for NAAT or viral culture.
- Wet mount can be used for a vaginal swab specimen for BV if discharge is present.
- Collection of serum samples should be evaluated, preserved for subsequent analysis, and used as a baseline for comparison with follow-up serologic tests. Sera can be tested for antibodies to *T. pallidum*, HIV, and HBV. Decisions regarding the infectious agents for which to perform serologic tests should be made on a case-by-case basis.

## Treatment

The risk for a child acquiring an STI as a result of sexual abuse or assault has not been well studied. Presumptive treatment for children who have been sexually assaulted or abused is not recommended because the incidence of most STIs among children is low after abuse or assault, prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and regular follow-up of children usually can be ensured. However, certain children or their parent or guardian might be concerned about the possibility of infection with an STI, even if the health care provider has perceived the risk to be low. Such concerns might be an indication for presumptive treatment in certain settings and might be considered after all relevant specimens for diagnostic tests have been collected.

## Other Management Considerations

Children who are survivors of sexual assault or abuse are at increased risk for future unsafe sexual practices that have been

linked to higher risk for HPV acquisition (1426,1453) and are more likely to engage in these behaviors at an earlier age; therefore, ACIP recommends vaccination of these children at age ≥9 years if they have not initiated or completed HPV vaccination (see Human Papillomavirus Infections, Prevention) (<https://www.cdc.gov/vaccines/hcp/acip-recommendations/vaccine-specific/hpv.html>). Although HPV vaccine will not protect against progression of infection already acquired or promote clearance of the infection, the vaccine protects against HPV types not yet acquired.

## Follow-Up

If no infections were identified at the initial examination after the last suspected sexual exposure, and if this exposure was recent, a follow-up evaluation approximately 2 weeks after the last exposure can be considered. Likewise, if no physical examination or diagnostic testing was performed at the initial visit, a complete examination can be scheduled approximately 2 weeks after the last exposure to identify any evidence of STIs. In circumstances in which transmission of syphilis, HIV, HBV, or HPV is a concern but baseline tests for syphilis, HIV, and HBV are negative and examinations for genital warts are negative, follow-up serologic testing and examination approximately 6 weeks and <3 months after the last suspected sexual exposure is recommended to allow time for antibodies to develop and signs of infection to appear. In addition, results of HBsAg testing should be interpreted carefully because HBV can be transmitted nonsexually. Decisions regarding which tests should be performed should be made on a case-by-case basis.

## Risk for Acquiring HIV Infection

HIV has been reported among children for whom sexual abuse was the only known risk factor. Serologic testing for HIV should be considered for sexually abused children. The decision to test for HIV should involve the family, if possible, and be made on a case-by-case basis depending on the likelihood of infection in the assailant (1448,1454). Although data are insufficient concerning the efficacy of PEP among children, treatment is well tolerated by infants and children with and without HIV, and children have a minimal risk for serious adverse reactions because of the short period recommended for prophylaxis (1455).

## Recommendations for Postexposure HIV Risk Assessment of Children <72 Hours After Sexual Assault

Providers should do the following:

- Review local HIV epidemiology, assess risk for HIV in the assailant, and test for HIV.

- Evaluate the circumstances of the assault or abuse that might affect risk for HIV transmission.
- Perform HIV antigen or antibody testing (or antibody testing, if antigen or antibody testing is unavailable) during the original assessment and again at follow-up visits, in accordance with CDC guidelines (<https://stacks.cdc.gov/view/cdc/38856>). In considering whether to offer PEP, health care providers should consider whether the child can be treated soon after the sexual exposure (i.e., <72 hours), the likelihood that the assailant has HIV infection, and the likelihood of high compliance with the prophylactic regimen (1436). Potential benefit of treating a sexually abused child should be weighed against the risk for adverse reactions.
- Consult with a provider specializing in evaluating or treating children with HIV infection to determine age-appropriate dosing and regimens and baseline laboratory testing, if PEP is being considered.
- Discuss PEP with the caregivers, including its toxicity, unknown efficacy, and possible benefits, for children determined to be at risk for HIV transmission from the assault or abuse.
- Provided adequate doses of medication, if PEP is begun, to last until the follow-up visit 3–7 days after the initial assessment, at which time the child should be reevaluated and tolerance of medication assessed (139).

### Conflicts of Interest

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Christina Muzny reports other support from CDC, during the conduct of the study; grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases and Lupin Pharmaceuticals; personal fees from Lupin Pharmaceuticals, PhagoMed, Cepheid, and Beckton Dickinson; and personal fees and other support from Roche Diagnostics, Abbott Molecular, and BioFire Diagnostics, outside the submitted work. Hilary Reno reports grants from Hologic, outside the submitted work. Christine Johnston reports other support from CDC, during the conduct of the study; received research funding from Sanofi-Pasteur; royalties from UpToDate; and personal fees from MedPace, Gilead, AbbVie, and UpToDate, outside the submitted work.

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## STI Treatment Guidelines, 2021, Work Group Members

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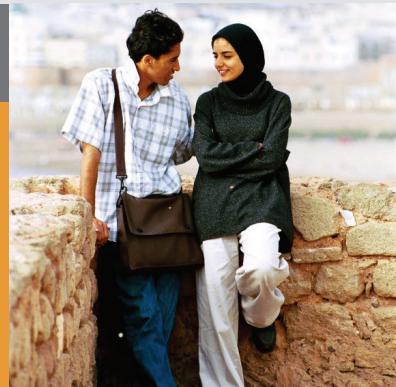
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# Sexually transmitted infections

## fact sheet

*More than 1 million people acquire a sexually transmitted infection every day.*



### Key facts

- ▶ More than 1 million people acquire a sexually transmitted infection (STI) every day.
- ▶ Each year, an estimated 500 million people become ill with one of 4 STIs: chlamydia, gonorrhoea, syphilis and trichomoniasis.
- ▶ More than 530 million people have the virus that causes genital herpes (HSV2).
- ▶ More than 290 million women have a human papillomavirus (HPV) infection.
- ▶ The majority of STIs are present without symptoms.
- ▶ Some STIs can increase the risk of HIV acquisition three-fold or more.
- ▶ STIs can have serious consequences beyond the immediate impact of the infection itself, through mother-to-child transmission of infections and chronic diseases.
- ▶ Drug resistance, especially for gonorrhoea, is a major threat to reducing the impact of STIs worldwide.

### What are sexually transmitted infections and how are they transmitted?

STIs are caused by more than 30 different bacteria, viruses and parasites and are spread predominantly by sexual contact, including vaginal, anal and oral sex.

Some STIs may be spread via skin-to-skin sexual contact. The organisms causing STIs can also be spread through non-sexual means such as blood products and tissue transfer. Many STIs – including chlamydia, gonorrhoea, hepatitis B, HIV, HPV, HSV2 and syphilis – can also be transmitted from mother to child during pregnancy and childbirth.

A person can have an STI without having obvious symptoms of disease. Therefore, the term “sexually transmitted infection” is a broader term than “sexually

transmitted disease” (STD). Common symptoms of STDs include vaginal discharge, urethral discharge in men, genital ulcers, and abdominal pain.

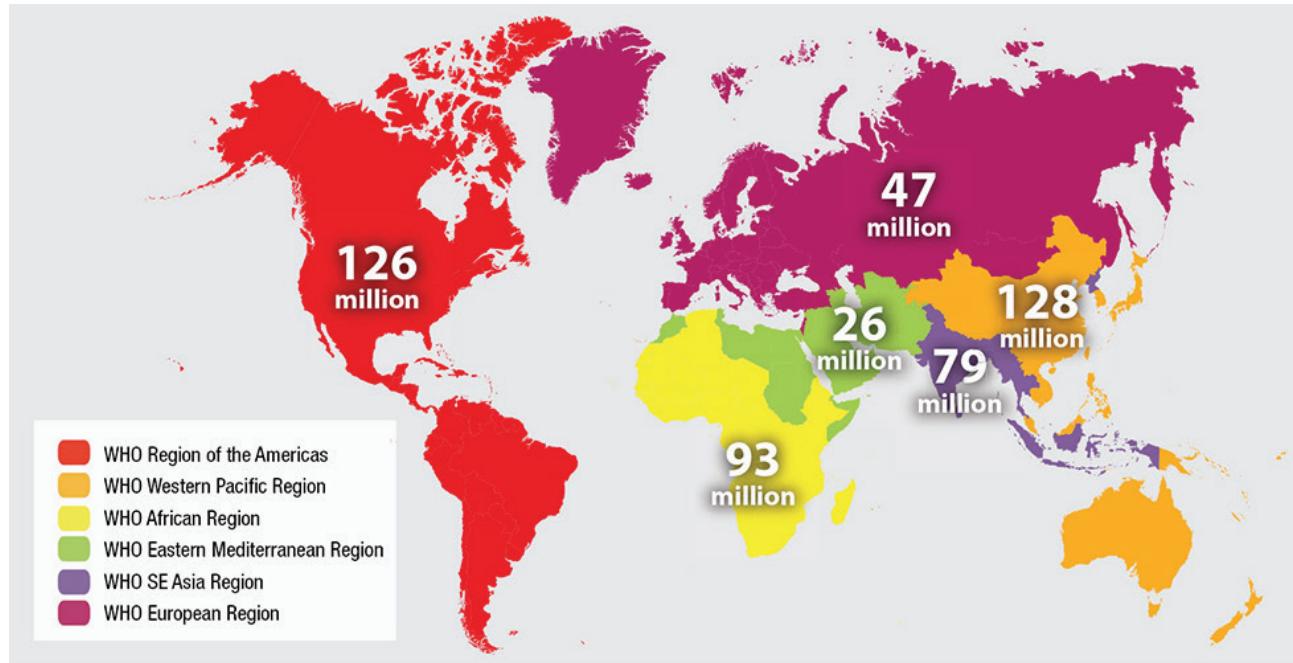
Eight of the more than 30 pathogens known to be transmitted through sexual contact have been linked to the greatest incidence of illness. Of these 8 infections, 4 are currently curable: syphilis, gonorrhoea, chlamydia and trichomoniasis. The other four are viral infections and are incurable, but can be mitigated or modulated through treatment: hepatitis B, herpes, HIV, and HPV.

### Scope of the problem

STIs have a profound impact on sexual and reproductive health worldwide, and rank among the top 5 disease categories for which adults seek health care.

More than 1 million people acquire a sexually transmitted infection every day. Each year, an estimated 500 million people acquire one of four sexually transmitted infections: chlamydia, gonorrhoea, syphilis and trichomoniasis. More than 530 million people are living with HSV2. More than 290 million women have an HPV infection, one of the most common STIs.

#### Estimated new cases of curable sexually transmitted infections (gonorrhoea, chlamydia, syphilis and trichomoniasis) by WHO region, 2008



STIs can have serious consequences beyond the immediate impact of the infection itself.

- Some STIs can increase the risk of HIV acquisition three-fold or more.
- Mother-to-child transmission of STIs can result in stillbirth, neonatal death, low birth weight and prematurity, sepsis, pneumonia, neonatal conjunctivitis, and congenital deformities. Syphilis in pregnancy leads to approximately 305 000 fetal and neonatal deaths every year and leaves 215 000 infants at increased risk of dying from prematurity, low birth weight or congenital disease.
- HPV infection causes 530 000 cases of cervical cancer and 275 000 cervical cancer deaths each year.
- STIs such as gonorrhoea and chlamydia are major causes of pelvic inflammatory disease, adverse pregnancy outcomes and infertility.

as well as against unintended pregnancies. These include:

- comprehensive sexuality education, STI and HIV pre- and post-test counselling;
- safer sex/risk-reduction counselling, condom promotion; and
- interventions targeted at key and vulnerable populations, such as adolescents, sex workers, men who have sex with men and people who inject drugs.

In addition, counselling can improve people's ability to recognize the symptoms of STIs and increase the likelihood they will seek care or encourage a sexual partner to do so. Unfortunately, lack of public awareness, lack of training of health workers, and long-standing, widespread stigma around STIs remain barriers to greater and more effective use of these interventions.

#### Barrier methods

When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe, but are not used as widely by national programmes as male condoms.

## Prevention of STIs

### Counselling and behavioural approaches

Counselling and behavioural interventions offer primary prevention against STIs (including HIV),

## Diagnosis of STIs

Accurate diagnostic tests for STIs are widely used in high-income countries. These are especially useful for the diagnosis of asymptomatic infections. However, in low- and middle-income countries, diagnostic tests are largely unavailable. Where testing is available, it is often expensive and geographically inaccessible; and patients often need to wait a long time (or need to return) to receive results. As a result, follow up can be impeded and care or treatment can be incomplete.

The only inexpensive, rapid blood test currently available for an STI is for syphilis. This test is already in use in some resource-limited settings. The test is accurate, can provide results in 15 to 20 minutes, and is easy to use with minimal training. Rapid syphilis tests have been shown to increase the number of pregnant women tested for syphilis. However, increased efforts are still needed in most low- and middle-income countries to ensure that all pregnant women receive a syphilis test.

Several rapid tests for other STIs are under development and have the potential to improve STI diagnosis and treatment, especially in resource-limited settings.

## Treatment of STIs

Effective treatment is currently available for several STIs.

- Three bacterial STIs (chlamydia, gonorrhoea and syphilis) and one parasitic STI (trichomoniasis) are generally curable with existing, effective single-dose regimens of antibiotics.
- For herpes and HIV, the most effective medications available are antivirals that can modulate the course of the disease, though they cannot cure the disease.
- For hepatitis B, immune system modulators (interferon) and antiviral medications can help to fight the virus and slow damage to the liver.

Resistance of STIs – in particular gonorrhoea – to antibiotics has increased rapidly in recent years and has reduced treatment options. The emergence of decreased susceptibility of gonorrhoea to the “last line” treatment option (oral and injectable cephalosporins) together with antimicrobial resistance already shown to penicillins, sulphonamides, tetracyclines, quinolones and macrolides make

gonorrhoea a multidrug-resistant organism. Antimicrobial resistance for other STIs, though less common, also exists, making prevention and prompt treatment critical.

## STI case management

Low- and middle-income countries rely on syndromic management, which is based on the identification of consistent groups of symptoms and easily recognized signs (syndromes) to guide treatment, without the use of laboratory tests. This approach, which often relies on clinical algorithms, allows health workers to diagnose a specific infection on the basis of observed syndromes.

Syndromic management is simple, assures rapid, same-day treatment, and avoids expensive or unavailable diagnostic tests. However, this approach misses infections that do not demonstrate any syndromes - the majority of STIs globally.

## Vaccines and other biomedical interventions

Safe and highly effective vaccines are available for two STIs: hepatitis B and human papillomavirus (HPV). These vaccines have represented major advances in STI prevention. The vaccine against hepatitis B is included in infant immunization programmes in 93% of countries and has already prevented an estimated 1.3 million deaths from chronic liver disease and cancer.

HPV vaccine is available as part of routine immunization programmes in 45 countries, most of them high- and middle-income. HPV vaccination could prevent the deaths of more than 4 million women over the next decade in low- and middle-income countries, where most cases of cervical cancer occur, if 70% vaccination coverage can be achieved.

Research to develop vaccines against herpes and HIV is advanced, though no viable vaccine candidates for either infection have yet emerged. Research into vaccines for chlamydia, gonorrhoea, syphilis and trichomoniasis is in earlier stages of development.

Other biomedical interventions to prevent some STIs include adult male circumcision and microbicides.

- Male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60% and provides some protection against other STIs, such as herpes and HPV.

- Tenofovir gel, a microbicide with the potential to allow women to actively avert HIV acquisition, reached “proof of concept” stage in clinical trials in 2010. Further clinical research to support regulatory approval of its safety and effectiveness is underway.

## Current efforts to contain the spread of STIs are not sufficient

### Behaviour change is complex

Despite considerable efforts to identify simple interventions that can reduce risky sexual behaviour, behaviour change remains a complex challenge. Research has demonstrated the need to focus on carefully defined populations, consult extensively with the identified target populations, and involve them in design, implementation and evaluation.

### Health services for screening and treatment of STIs remain weak

People seeking screening and treatment for STIs face numerous problems. These include limited resources, stigmatization, poor quality of services, and little or no follow-up of sexual partners.

- In many countries, STI services are provided separately and not available in primary health care, family planning and other routine health services.
- In many settings, services are often unable to provide screening for asymptomatic infections, lacking trained personnel, laboratory capacity and adequate supplies of appropriate medicines.
- Marginalized populations with the highest rates of STIs – such as sex workers, men who have sex with men, people who inject drugs, prison inmates, mobile populations and adolescents – often do not have access to adequate health services.

## WHO response

WHO develops global norms and standards for STI treatment and prevention, strengthens systems for surveillance and monitoring, including those for drug-resistant gonorrhoea, and leads the setting of the global research agenda on STIs.

Our work is guided by Millennium Development Goals 4, 5 and 6, the global strategy for the prevention and control of STIs adopted by the World Health Assembly in 2006 and the 2010 United Nations Secretary-General’s Global Strategy for Women’s and Children’s Health, which highlights the need for a comprehensive, integrated package of essential interventions, including information and services for the prevention of HIV and other sexually transmitted infections.

WHO works with countries to:

### Scale-up effective STI services including:

- STI case management and counseling
- syphilis testing and treatment, in particular for pregnant women
- hepatitis B and HPV vaccination.

Promote strategies to enhance STI-prevention impact including:

- integrate STI services into existing health systems
- promote sexual health
- measure the burden of STIs
- monitor and respond to STI antimicrobial resistance.

Support the development of new technologies for STI prevention such as:

- point-of care diagnostic tests for STIs
- additional drugs for gonorrhoea
- STI vaccines and other biomedical interventions.

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# Syphilis: then and now

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## Abstract

Getting to know the history of syphilis should begin with an attempt to establish the original source of its spread throughout the world. The dispute about the origin of syphilis, a sexually transmitted infection caused by *Treponema pallidum* (subspecies *pallidum*), had not been resolved even as late as in the twenty-first century, and to this day the supporters and opponents of the thesis that syphilis was brought to Europe by Christopher Columbus' sailors have been fighting without solid and sustainable foundations. The French named syphilis "the Neapolitan disease", while the Italians called it "the French disease".

**Key words:** syphilis, sexually transmitted infection, history.

## Introduction

According to the definition from 1929, "Sexually transmitted diseases, also called venereal diseases (after Venus, the Roman goddess of love), shall be understood as genital diseases caused by a sexually transmitted infection". Currently, the term sexually transmitted diseases (STDs) is more frequently used. These diseases, more often defined as venereal diseases, result from behaviours influenced by socio-economic, psychological and cultural factors.

In 2018, 33,927 newly diagnosed cases of syphilis were reported in the 29 EU/EEA states, comprising 7.0 cases per 100,000 people in countries with a comprehensive surveillance system. The highest rates were noted in Malta, Luxembourg, the United Kingdom and Spain, 17.9, 17.1, 12.6 and 10.3 cases per 100,000 people, respectively. The lowest rates were observed in Croatia, Estonia, Italy, Portugal and Slovenia, with fewer than 3 cases per 100,000 people. The incidence rates of syphilis were nine times higher among men than among women, and the peak incidence was among those aged 25–34 years (29 cases per 100,000 people) [1].

The spectrum of sexually transmitted infections, apart from classic syphilis and gonorrhoea, encompasses a wide range of aerobic and anaerobic bacteria, viruses, protozoans, fungi and even insects.

Getting to know the history of syphilis should begin with an attempt to establish the original source of its spread throughout the world. As it has already been mentioned, *Treponema pallidum* is a Gram-negative bacteria. It does not absorb stain and therefore should be visualised using dark-field microscopy. Although its virulent factors have not been fully understood yet, we know that it enters the body through direct contact, e.g. abrasions in the skin or sexual contact, it reaches the nearest lymph nodes and spreads through the blood. The basic pathology of syphilis is vasculitis. The disease has been divided into several stages [2–4].

A primary lesion occurs at the site of spirochaete penetration 3–4 weeks after incubation as a hard infiltration which turns into an ulcer (*ulcus primarium*).

Ulcers are single, flat, shallow, round or oval, 0.5–1.5 cm in diameter with even edges, a slightly recessed even bottom, shiny surface (mucoid secretion), and infiltrated base. Ulcer disappears, but it seems, that infiltrated base disappears.

It is most often located on the genitalia (female labia, posterior commissure, vaginal wall, cervix and male inner plate of prepuce, glans penis), as well as on the lips, tongue, buccal mucosa, anus and fingers. Enlarged lymph node regions are also observed for several weeks. They are hard, painless, without packages and necrosis, mobile relative to the substrate, with skin unchanged above [5].

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Secondary syphilis results from haematogenous dissemination of *T. pallidum*. It is characterised by severe bacteraemia, skin rash, and a rash on oral mucosa. Enlarged lymph nodes are also for a few months (large, hard, painless, without packages and conglutination, the skin remains unchanged). In the case of early second-stage syphilis, a macular rash occurs most often. There, skin eruptions (spots of similar size – from small to large and of the same round or oval shape) are observed evenly and symmetrically across the body, most often on the side of the torso and on the flexor side of the forearms. They disappear spontaneously after 2–3 weeks without peeling and without trace, or the disease recurs [6, 7].

Late syphilis (*lues tarda*) occurs a few years after infection, in untreated or insufficiently treated patients.

Another problem, more common in the past than today, is congenital syphilis. It is caused by a spirochete acquired by the foetus in the uterus before birth after the 16<sup>th</sup> week of pregnancy. Early congenital syphilis (*lues congenita recens*) is characterised by profuse rashes: macular (large, confluent and irregular patches, mainly on the buttocks, face, palms and soles), papular (scattered, most often on the face and buttocks), pustular and blistering (palms and feet, oozing erosions with an infiltrated base). In addition, there are infiltrated changes around natural orifices in the form of radial cracks, contributing to the formation of the so-called Parrot's scars, and dark red confluent infiltrates on the buttocks, palms and soles with a taut shiny surface, the so-called "Lacquered buttocks". However, the first symptom is usually coryza syphilitica as a consequence of ulceration of the nasal mucosa, contributing to respiratory and sucking disorders as the disease progresses. In the absence of treatment, there may be permanent bone deformation, the so-called "saddle nose". About 30% of infected children suffer from Parrot's palsy, which results in motor inertia of the upper limbs and contracture of the lower limbs. In addition, hepatosplenomegaly, hyperbilirubinemia, elevated liver tests and haemolytic anaemia are observed [4].

Late congenital syphilis (*lues congenita tarda*) is most commonly asymptomatic. About 20% of infected children develop interstitial keratitis (keratitis parenchymatosa) between the ages of 5 and 30, Hutchinson teeth; Parrot's scars around the mouth and anus; hearing impairment and mental retardation [8, 9].

It is worth mentioning that the spirochete *Treponema pallidum* was identified in 1905 by Fritz Richard Schaudinn and Paul Erich Hoffmann. On this basis, August von Wassermann developed the first serologic test for the diagnosis of syphilis (the Wassermann reaction test) [10].

### The history of syphilis

Being aware of the consequences of the disease, we can delve into the past of syphilis, its appearance in Europe, and connections with Polish history. The dispute about the origin of this disease had not been resolved

even as late as in the twenty-first century, and to this day the supporters and opponents of the thesis that syphilis was brought by Christopher Columbus' sailors have been fighting without solid and sustainable foundations. It is likely that infected Indians were taken on board caravels, or sailors "spreading" to a new land were infected by beautiful, red-skinned women. Another idea, similar in time, talks about the army of Charles VIII and its impact on the spread of syphilis in Europe. On 1 September 1494, King Charles VIII of France invaded Italy with a multinational army composed mostly of mercenaries [10].

On the last day of the year, the French troops entered Rome, just abandoned by the Spanish and Italian troops. They remained there for almost a month, carousing and engaging in debauchery. In January, the changed army left for Naples, with loose manners and discipline, followed directly by a cohort of beggars and prostitutes. Naples was captured without a single shot fired, and the winners could indulge in the pleasures of another Italian city. Due to the lack of other permanent achievements, the French took away the seeds of Revival from the attacked lands. But there were also other seeds, much less pleasant, that Charles VIII's soldiers collected during their debaucherous revels – the seeds of a terrible and unknown disease, so unknown that it had no name. The French named syphilis "the Neapolitan disease", and the Italians called it "the French disease" [11, 12]. The first descriptions of the disease come from the Battle of Fornovo (1495). It was then that the military doctor, Cumane, reported what he observed: "many of the knights or infantry had spots on their faces and all over their bodies caused by the boiling of the four humours. Similar to millet grains, they usually appeared on the foreskin, on its inner surface, or on the glans, slightly itchy. Often, a single spot in the form of an innocent bubble appeared at first, but scratching it resulted in a penetrating ulcer. A few days later, the patients experienced incredible pain in their arms, legs and feet, as well as a sudden ejection of large spots [...] [present] for a year or longer if no treatment was applied" [13]. Another doctor, also taking part in the Battle of Fornovo, observed people who lost their eyes, noses, hands and feet as a result of the disease. In addition, when conducting an autopsy of a woman affected by the French disease, he found bone tuberosity. This is when this cruel disease began to be observed. At the end of the fifteenth century, the Spanish published the first extensive medical treatises on this issue, e.g. Marcel Morel's doctoral dissertation. Regardless of the country of origin, all the people writing about syphilis noticed its connection with the sexual act, which is why the first advice concerned abstinence and avoiding intercourse with infected women. Other pieces of advice were more practical. It was recommended to carefully wash the genitals with warm water or white wine after intercourse, and in the case of infection, also with herbal solutions, to sprinkle them with powder composed of,

among others, litharge (lead oxide), gold and cerussite (lead carbonate). Above all else, however, it was believed that the symptoms of the disease were divine punishment for sins, and one should not fight with it. Therefore, infected people were treated like those suffering from leprosy. They were isolated and hardly anyone wanted to have any contact with them.

Another way of dealing with syphilis by the then doctors was to remove ulcers by cauterisation. For this purpose, they used ointments containing mercury. In patients, the lesions were rubbed with ointment once or twice a day and the patients were locked in a steam bath at a very high temperature. The treatment lasted from 20 to 30 days and was so painful that most of the patients preferred death, all the more so because this barbaric procedure was effective for only one in one hundred patients.

The beginnings of “the Neapolitan disease” made all the Europeans terrified. After the description of the first cases, there came a time to name the disease. Syphilis appeared. Hieronymus Fracastorius was born in Verona in 1483. A colleague of Copernicus at the University of Padua where he studied medicine and philosophy at the same time, he was the author of many works. He died, famous and respected, in 1553 near his birthplace. His work “*Syphilis sive morbus gallicus*” (“Syphilis or the French Disease”) brought him fame. It was a long Latin poem telling the story of Syphilus, a shepherd who insulted the god of sun by knocking down his altars, for which he was punished with a venereal disease. The inhabitants of the surrounding villages named the disease “syphilis” in memory of the one who was first infected. The name, however, was not accepted in everyday life until the end of the eighteenth century [14, 15].

Over the centuries, syphilis appeared both in simple burgher houses and in the chambers of European kings and rulers. Since its occurrence was commonly associated with prostitution, the approaches to widespread worldwide prostitution changed. Thus, this “oldest profession in the world” was no longer treated with tolerance. There were orders to put prostitution under police supervision along with the obligation for women to undergo medical examination once a week. Despite all of this, the disease appeared in many forms, depending on geographical, weather and demographic conditions. The attempts to standardise legal regulations related to prostitution in France were undertaken in the twentieth century, e.g. by creating a decree of the Ministry of the Interior addressed to the prefects, confirming the regulation of prostitution (1940), and a law “for prevention and combating venereal diseases”, implementing, in particular, the obligation for doctors to report cases of venereal diseases to the health authorities (1942).

Syphilis affected so many people that it was impossible to mention their names. It was even more embarrassing among royal families than among lower classes. On

many occasions, for fear of infection, every person “entering” the bed of a ruler was examined and controlled for the signs of any disease. It was also the case that the rulers were infected by their lovers, and then, unaware, gave this quite an original “gift” to their spouses. In this way, syphilis had unlimited possibilities to spread among upper classes that were not using, at least officially, the services of women of easy virtue. For a long time, the infertility of monarchs was attributed to syphilis, however, as it was later scientifically proven, there was no direct link between these cases. Nevertheless, the fact is that a woman suffering from syphilis is much more likely to have a miscarriage or give birth to a dead baby.

The history of syphilis also has its influence and a rich collection of literature in Poland. A well-known medical historian, Kazimierz Lejman, wrote about it. The most extensive outline of syphilis was presented by Andrzej Stapiński in his book titled “*Zwalczanie kity i rzeżączki w Polsce*” (“Fighting Syphilis and Gonorrhoea in Poland”).

The first records of “the Neapolitan disease” in Polish lands dated back to the early fifteenth or even fourteenth century and it is still under discussion today on the origin of syphilis from America. The speed of spreading the disease in Europe suggests that it was brought to Polish lands at the same time. Here it was called a court disease, but the ways of dealing with it proved that it also affected the common people. As early as in 1528, behind the city walls, a hospital for venereal patients was established in Krakow. It resembled today’s medical facilities in name only. The name isolation facilities would be more appropriate here. It was established in the fashion of a Paris institution of the same purpose. In the sixteenth century, like in Western Europe, treatment was based on rubbing mercury ointments. Due to the fact that it was expensive and folk healers and doctors had no experience, another way of dealing with the disease was invented. The naked patient was buried up to his neck in dung, which was to “pull out” the disease [16, 17]. When new isolation facilities where the disease was treated with the use of mercury appeared, this method was slowly abandoned, yet it survived until the eighteenth century [18, 19]. Such a facility was established in Warsaw in 1590 by the Jesuit Piotr Skarga. Syphilis was the subject of many medical dissertations, e.g. “*Przymiot*” (“Attribute”) by Wojciech Oczko. It explains the essence of the disease on the basis of the so-called humoral theory. It asserts that the human body consists of four humours: blood, phlegm, yellow bile and black bile, and their mutual balance is important for health. Any humoral disorder is the cause of many diseases. This is why syphilis was treated with blood drops at that time. There are no descriptions of syphilis in Poland from the seventeenth century. However, that does not mean that the problem was at least half solved. The descriptions from hospitals conducting 3-month treatment therapies for patients prove that syphilis survived and flourished in the eighteenth century. The nineteenth century brought another problem which was

difficult to solve – children with syphilis were born. Earlier live births with similar symptoms were probably not yet associated with this disease. These children were abandoned, and their number was so large that special wards were established in hospitals for them.

Changes resulting from invasions by oppressors to Polish lands did not have any significant impact on the history of syphilis. It developed freely, claiming more victims.

The life of the rulers of Polish lands was also not free from the risk of being infected with syphilis. The high probability of infection concerned Alexander Jagiellon (died in 1506), who led a very debaucherous lifestyle. Due to the uncertainty of the cause of his death, King Władysław IV Vasa was also thought to be infected with syphilis. The most famous example of syphilis among Polish rulers is still considered to be Marie de la Grange d'Arquien, Queen of Poland, known also by the diminutive form "Marysieńka". She was probably infected by her first husband, Jan Zamoyski. However, this did not prevent Jan Sobieski from loving her to death and writing letters to her, which became a masterpiece of erotic lyricism.

In Poland, as we can see, the history of "the Neapolitan disease" did not differ significantly from the place of its first reign. Each country has an episode in its history, and only the names of the infected people change.

Finally, it is worth taking a look at the current situation of syphilis since it will also be a part of our history 1 day. The incidence of syphilis, like of most sexually transmitted diseases, is increasing. Recent epidemiologic data show an average increase of 9000 cases per quarter. Serological tests, the best known of which is the Wassermann test (based on IgG class antibodies) [20] allow for early diagnosis of the disease. However, it should be borne in mind that the oldest test used to diagnose syphilis is VDRL. It was invented before World War I, with its first iteration developed by August Paul von Wasserman with the aid of Albert Neisser in 1906. The medication of choice is penicillin, which should be administered for 3 weeks to patients who have had syphilis for longer than a year. It was discovered in 1943, which has forever changed the fate of the patients. The methods presented earlier in the text were more often "punishment for sins" than for relief of suffering, and their final effect was not as good as expected. Mercury and guaiacum treatments were the two alternatives in the fifteenth and sixteenth century, and scientists were proving their effectiveness interchangeably. The historical significance of treating syphilis with Salvarsan ("the arsenic that saved") or compound 606 (the name derives from the 606<sup>th</sup> compound injected by Ehrlich into syphilis-infected rabbits in 1909) should also be emphasised. Due to its adverse effects, it was then withdrawn and replaced with Neosalvarsan or compound 914 (again after the number of injections into rabbits) [21].

## Syphilis in the artistic context

When discussing the history of syphilis, the artistic context dating back to the sixth century must not be overlooked: a Peruvian jug depicted a mother suffering from syphilis, with a characteristic saddle nose and superior incisive teeth with notches on their free margins.

In Europe, the German artist Albrecht Dürer depicted in 1496 the image of a mercenary whose skin bears multiple sores, and a text by a physician Theodorus Ulssenius warning against the new disease, also describing its signs and symptoms [22, 23]. An artwork by Sebastian Brandt also comes from the same year. It depicts the Virgin Mary and the Christ Child shooting light arrows to punish or heal those infected with syphilis [22, 24].

Other prominent pictures include those by Jacques Lanier from the seventeenth century, Luca Giordano, Sadeler [24] and a portrait of Gerard de Lairesse painted by Rembrandt in the seventeenth century, clearly emphasising the effects of syphilis, namely the saddle nose [25].

"Inheritance" by the Norwegian painter Edvard Munch portrays a young crying mother holding a child with symptoms of syphilis.

The artwork "Les Demoiselles d'Avignon" by Pablo Picasso, originally called "The Wages of Sin", features a sailor among prostitutes, and a medical student holding a skull as a symbol of mortality.

The symptoms of syphilis are also present in Krakow works of art. Dermatologist and venereologist Franciszek Walter noticed the following skin lesions among probably fifteen-century-old inhabitants of Krakow, carved by Wit Stwosz with senile warts (verruca senilis), basal cell carcinoma (epithelioma), rosacea (in Walter: "rubella", acne rosacea), or varicose veins of the lower limbs (varices extremitatum inferiorum) [16, 26].

In 1932, Walter also noticed symptoms of congenital syphilis in "The Arrest of Jesus" scene in a figure called by Walter, a Pharisee with a huge wide and hairless square skull, with a huge convex forehead and clearly protruding frontal bumps (tubera frontalia). He noticed "eyes in deeply set eye sockets, with protruding bone rims", "exophthalmos (exophthalmus)", "convergent strabismus (strabismus convergens)", "there are eyebrows, but no eyelashes", "narrow and sunken upper lip due to lack of base bone", "much paler right pupil, blurred cornea pattern", and finally, what is most characteristic, "saddle nose" (in other words: "bulldog nose", "ram", "blunt", "binocular"). On the other hand, in the "Christ Among Scientists" scene, congenital syphilis can be seen in a scientist with a saddle nose. In the same year, Walter began collecting photographic documentation of his patients' tattoos, which may indicate Walter's interest in medicine, psychology, sociology or arts [16].

In the 14<sup>th</sup>-century basement of the building situated at Rynek Główny 23 in Krakow, a keystone with a face described as "negroid" or "perfect understanding of cari-

cature" has been preserved. Saint Peter's nose with its characteristic "saddle nose" is also worth mentioning [16].

## Summary

In this way syphilis created its own history and the map of Europe. It was a cruel yet extremely just "ruler" that affected both the poor and the rich. It influenced the number of offspring and, as one of many diseases, was recorded in the works of the scientists, writers and painters of the day. It was a part of life and our history, although more embarrassing than momentous events. However, this is not a reason to forget about its strong influence.

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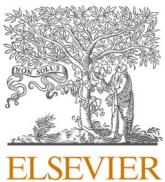
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## Conflict of interest

The authors declare no conflict of interest.

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## Review

## The outbreak of monkeypox 2022: An overview

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## ABSTRACT

On May 6, 2022 an outbreak of monkeypox (MPX) was confirmed in the United Kingdom, originating from a British resident who had travelled to Nigeria. As of May 21, 2022, 92 cases have been confirmed worldwide, from 13 countries where monkeypox virus (MPXV) is not endemic. Reported cases thus far have mainly but not exclusively been identified among gay and bisexual men aged 20–50. MPXV is a viral zoonosis transmitted to humans via contacting or eating an infected animal, and direct contact with natural host's blood and body fluids. In addition to contacting with a patient's respiratory droplets, lesions, body fluids and polluted personal objects. Symptoms including shivers, headaches, fainting, backaches, and myodynias do not have any specific characteristics making it difficult to establish a proper diagnosis. Nevertheless, lymphatic hyperplasia, one of the most common symptoms of monkeypox, can be useful for diagnosing the disease. Clinical symptoms help establish the suspicion of monkeypox. However, in the absence of confirmed diagnostic tests it is very difficult to verify the disease and determine its cause based on clinical symptoms alone. There are numerous methods for detecting MPX, involving genetic, phenotypic, immunological methods, and electron microscopy. These tests require modern equipment and expert hands, which may not be available in developing countries where this disease is prevalent. Currently, there is no definite treatment for MPX. CDC recommends administering the smallpox vaccine within 4 days of exposure which may prevent the disease from happening, and within 2 weeks to reduce symptoms severity. To promptly identify patients and prevent further spreading, physicians should be aware of the travel or contact history of the patient with compatible symptoms.

## 1. Introduction

On May 6, 2022 an outbreak of monkeypox (MPX) was confirmed in the United Kingdom (UK), originating from a British resident who had travelled to Nigeria, where the disease is endemic, and while there, presented symptoms consistent with on April 29, 2022. This person returned to the UK on May 4, importing the index case of the outbreak into the country [1].

As of May 21, 2022, 92 cases have been confirmed worldwide, from 13 countries where monkeypox virus (MPXV) is not endemic (UK, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, USA) [2]. As of May 22, 2022, the total number of countries have confirmed outbreaks has risen to 15. The United Arab Emirates (UAE) is the first Arab country to report an infected case on May 24 [3]. No deaths have been reported so far [2], and Belgium has become the first country to introduce a compulsory 21-day MPX quarantine [4].

MPXV was first isolated and identified in 1958 when monkeys transported from Singapore to Denmark for research purposes got a vesicular disease. Hence the name "monkeypox" [5]. However, rodents such as squirrels and giant pouched rats, which are hunted for food, represent the largest animal reservoirs for the virus [6].

The first human case was discovered in August 1970 when the virus was isolated from a 9-year-old child in rural areas of Democratic Republic of Congo (DRC) suspected of having smallpox [7].

Since 1970, human cases of MPX have been reported in 11 African countries [2,8], with a median age of 31 years [9].

A small number of cases have been recorded before outside of Africa [8]. In the current outbreak, the virus was found for the first time in some patients who had no clear link to West and Central Africa [2].

Reported cases thus far have mainly but not exclusively been identified among gay and bisexual men aged 20–50 [2], but it is uncertain if sexual behaviors making it easier to spread, or it is just a coincidence [10]. The vaccinia virus which is used to provide cross-protection

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against smallpox is proven to spread through sexual contact, this is largely due to direct contact with the infected rash [11].

## 2. Virology

MPXV is a lipoprotein membrane-enveloped double-helix DNA virus of the genus Orthopoxvirus, that belongs to the Poxviridae family and the chordopoxvirinae subfamily [8,9,12]. The Poxviridae is an ancient virus family that has been found in insects, reptiles, birds, and mammals, and is thought to form visible “pox” prior to vertebrate-invertebrate divergence [13,14].

Although the poxviruses genome contains all requirement proteins to replicate, transcribe, assembly and exit, it needs infected individuals' ribosomes to translate mRNA [12].

Along with MPXV, there are three more types of orthopoxvirus that also effect humans, including variola major virus -the cause of smallpox-, variola minor virus (Variola alastrim), and cowpox virus (vaccinia) [9].

MPXV is considered a large virus which measure about 200–250 nm with the appearance “brick-like” or ovoid shape [12].

MPXV has two distinguished hereditary subgroups, the West African and the Central African (Congo Basin) which motivates more serious infection and is believed to cause a higher infective possibility. In spite of the fact that there are different geographical incidence locations between the two virus categories, they both occurred in the same country “Cameroon” [8,9].

The virus's original source is wild animals. It can be found in a variety of mammals including squirrels, mangabey monkeys and Gambian rats. Even though the essential host continues to be not clear, the rodents are believed to be the host reservoir rather than monkeys [9,13,15].

Human MPXV transmission happens in two ways, either from animal-to-human or human-to-human. Aerosol transmission has been demonstrated between animal populations [9]. Contacting with a patient's respiratory droplets, lesions, body fluids and polluted personal objects support the virus spreading among peoples. Furthermore, hospital-acquired transmission has been confirmed, whereas intercourse transmission is suspected for the patient with genital MPXV lesions. However, zoonotic transmission can exist if people contact or eat an infected animal, In addition to direct connect with natural host's blood and body fluids [8,13].

## 3. Clinical manifestations

MPXV has an incubation period ranging from five days to three weeks [9,16], and the symptoms can last for nearly 2–5 weeks. Early symptoms include shivers, headaches, fainting, backaches, and myodynna, but they are not specific [9].

The most common symptoms observed before the the rash development are fever, restlessness and lymphadenopathy [16]. Human MPX has similar clinical features to ordinary and modified smallpox [16,17], but generally more moderate [18]. As swollen lymph nodes are not a common sign of smallpox and are seen in 90% of MPX patients [9]. They are considered a distinctive hallmark of MPX. These enlargements can be observed in the neck, the groin and submandibular areas [16].

During the five days following the fever, various sizes of rashes develop, initially on the face and then spreading across the trunk area and extremities. The rashes often appear on the palms and soles of the feet [9]. These lesions measure approximately 0.5 cm in diameter, and some can reach up to 1 cm [18]. Exanthems progress through different developmental phases, resolving into crusts that fall off during the healing phase [9]. Lesion co-infection is recurrent and plays a major role in future skin marking [17].

While MPX symptoms are less severe than those of smallpox, it is still considered a fatal disease, that causes death at a fluctuating rate of up to 10% [9]. Death usually occurs within the second week of the infection [16]. The risk is higher in children and young adults, and the disease can take a severe course in immunocompromised patients [19]. The disease

can present with numerous complications, such as co-infections, respiratory disorders, encephalitis, blindness-related keratitis, and gastrointestinal symptoms like vomiting and diarrhea [9].

Smallpox vaccination can offer some protection against MPX and can alter the course of the disease. Studies between 1980 and 1990 indicated a change in the pathogenesis of human MPX, because more people without immunity to smallpox developed the disease. Moreover, the pathological picture was less severe in the vaccination group, and the skin infection was milder. This was in contrast to the unvaccinated, whose skin infection was more severe, with multiple forms and a higher probability of death [20–23].

Since the symptoms of MPX are varied and non-specific, many diseases can be included in a differential diagnosis. The differential diagnoses are: chickenpox (the most clinically similar disease), water warts, red measles, rickettsia disease, staphylococcus skin infections, bacillus anthracis, itch mites, syphilis, and drug reactions for non-infectious causes of rashes [24].

Since lymphatic adenopathy is one of the most frequently observed symptoms, which is a differential sign from other diseases, it is imperative to emphasize its importance in the initial examination of a suspected patient.

## 4. Diagnosis

In order to diagnose monkeypox, health providers should collect a proper specimen and send it carefully to a capable lab. Verifying human MPX virus relies on the sample type and the available laboratory tests [2].

As the illness symptoms are still difficult to identify and hard to minimize in low-income countries. It poses a world challenge since these areas are considered endemic with this disease [23].

The confirming techniques that are used for analyzing specimens and determine MPX include genetic, phenotypic and immunological methods [13]. Table 1 lists the diagnostic methods that can be used to identify human MPX. These approaches work better when are combined with the medical and epidemiological information including the patient's immunization history [23].

A detailed medical history with focus on specific information, such as recent traveling to an endemic area, vaccinating with the smallpox vaccine, along with linking clinical information to the existing symptoms, can be extremely directing to the disease diagnosis, but it is not sufficient to establish a definitive one. The golden test to establish the diagnose is the polymerase chain reaction. Beside its high accuracy and sensitivity, the viral DNA within the lesion persists constant for a long time if kept in a dark and comparatively cool atmosphere [23].

As Real-time PCR needs high quality labs which are hard to be found in low-resources countries. The upcoming technologies are reliable on to develop the PCR and qPCR to overcome their consequences and become available outside the large laboratories, which allows to have an accurate diagnostic tool within the reach of all medical staff, even those in poor countries.

Establishing the conditions source requires an antibody-based diagnosing. Immunological tests against orthopoxviruses have a cross-reactivity with other Orthopoxviruses. Still, these tests may be valuable when there is previous indication to explain the disease cause.

Although IgG alone cannot provide a definitive diagnosis to a patient who has been exposed to orthopoxvirus during his life through vaccination, IgM is considered more effective in diagnosing newly infections patients retrospectively [23,25].

MPX patients often pursue medical help at countryside health centers or hospices which are not provided with electricity [23]; therefore, it is requirement to improve the current tests so it can be used in developing countries where there is lack in resources and human performing.

**Table 1**

The diagnostic methods that can be used to identify human MPX.

	Genetic Methods	Phenotypic Methods	Immunological Methods	Electron Microscopy
Based on	PCR or qPCR [23].	Clinical diagnose [13].	<ul style="list-style-type: none"> <li>Sensitive detection of IgG or IgM antibodies against MPX using Elisa test.</li> <li>Immunohistochemical (IHC) to spot virus antigens [13].</li> <li>Increased antiviral antibodies and T-cell activation against MPX have been documented with disease onset [13].</li> <li>When a rash develops, IgM and IgG can be detected in serum about 5 days and more than 8 days in a row [13].</li> <li>If both IgM and IgG are present in unvaccinated persons with a history of rash and symptoms of severe disease, then an indirect diagnosis can be founded [13].</li> <li>The above methods are not considered qualitative for human MPX [13].</li> </ul>	Electron microscopy (EM).
Pros	<ul style="list-style-type: none"> <li>PCR is the standard test for detecting MPX-specific DNA sequences due to its high accuracy and sensitivity [2].</li> <li>For genetic testing, the recommended diagnostic samples are from cutaneous lesions (a smear from the surface of the lesion and/or exudate, or crusts of the lesion) or from a biopsy when possible [2,9].</li> </ul>	<ul style="list-style-type: none"> <li>possible diagnosing based on clinical signs is essential in order to expose suspected cases during examination [26].</li> </ul>	<ul style="list-style-type: none"> <li>Orthopoxviruses are indistinguishable from each other.</li> <li>Orthopoxviruses are indistinguishable from each other. Hence, it requires more specific testing diagnose [13].</li> </ul>	<ul style="list-style-type: none"> <li>Can distinguish Orthopoxvirus from herpes simplex virus.</li> <li>It gives evidence that mpox may belong to the Poxviridae family [13].</li> </ul>
Cons	<ul style="list-style-type: none"> <li>Highly sensitive examinations where there are justified concerns about sample contamination [23].</li> <li>These tests demand high-cost tools, reagents, and expert techniques [23].</li> </ul>	<ul style="list-style-type: none"> <li>According to a study conducted on a group of 645 individuals whose clinical diagnosis of MPX was not accompanied by a laboratory confirmation, it had a high sensitivity (93–98%) but low specificity (9%–26%) [24].</li> </ul>		

## 5. Prevention

Ever since the SARS outbreak in 2003 and even earlier, experts have realized the grave threat of zoonotic infections rising from constant remodeling of ecosystems, as per a report issued by the Institute of Medicine back in 2003 as a follow up to their 1992 report [27]. MPX is one such infection that is portrayed by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) as an emergent disease [28]. Preventing the spread of MPX is a war fought on many fronts:

On the ecological front, limiting humans' exposure to suspect host animals must be the first step as available evidence indicates that human-to-human transmission cannot sustain the continuance of an endemic without repeated zoonotic introductions [15]. This can be achieved by limiting people's dependence on hosts, in particularly rodents, as protein sources and instead relying on vegetarian alternatives [15]. In addition, urban expansion into reclaimed forest lands must be studied as to prevent displacement of reservoir animals [29]. Ecological prevention is especially important as future strains may not need repeated introductions if their transmissibility among humans increased [29]. Another front would be to protect at risk groups, which include health care workers, contacts of MPX patients, and workers in rural areas. CDC recommends that this protection can be achieved through small pox vaccines [9]. As data shows that the smallpox vaccine provides 85% protection against MPX via cross-immunity [30]. The problem regarding this approach is that first and second generations of smallpox vaccines can cause adverse side effects, which promotes the importance of developing third generation vaccines like INVAMUNE, which as for now, have proved efficient and safe in people infected with HIV or atopic dermatitis [31]. This is especially important in areas endemic to MPX as no accurate estimations of HIV infections exist in these countries [31].

In hospital settings, the CDC recommends that patients are to be isolated in negative pressure rooms and that health care professionals take adequate contact and droplet precautions [12]. This is the standardized response for a patient presenting with fever and disseminated vesicular or pustular rash [32]. Data shows that MPX is less transmissible among humans in comparison with smallpox, and the longest chain of infected individuals is around 6 patients [33].

## 6. Treatment

There is no specific treatment for MPX as to date [12]. CDC

recommends administering the smallpox vaccine within 4 days of exposure which may prevent the disease from happening, and within 2 weeks to reduce symptoms severity [12]. In immunocompromised patients, first and second generations smallpox vaccines are contraindicated, and are replaced with vaccinia immune globulin [32]. FDA approved Smallpox antivirals tecovirimat and brincidofovir can be used to treat MPX but there are no studies that prove their efficacy [12,32]. Other antivirals that show promise are Cidofovir, CMX-001, and ST-246 [33].

In conclusion, we should ask whether the virus has developed new properties that allow it to spread rapidly, and we should reconsider the decision to discontinue the national smallpox vaccination programs in many countries. Moreover, the most important questions are: Is this synchronization in the spread of the current hepatitis in children and MPX just a coincidence? Is there any possible connection with the COVID-19 Pandemic?

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### Author contribution

All authors contributed in all the phases of preparing the paper.

### Registration of research studies

It's a literature review; not a clinical trial.

### Guarantor

Prof. Dr. Zuheir Alshehabi.

### Consent

This article is a narrative review.

## Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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# Trichomoniasis - CDC Fact Sheet



## Most people who have trichomoniasis do not have any symptoms.

### What is trichomoniasis?

Trichomoniasis (or “trich”) is a very common sexually transmitted disease (STD). It is caused by infection with a protozoan parasite called *Trichomonas vaginalis*. Although symptoms of the disease vary, most people who have the parasite cannot tell they are infected.

### How common is trichomoniasis?

Trichomoniasis is the most common curable STD. In the United States, an estimated 3.7 million people have the infection. However, only about 30% develop any symptoms of trichomoniasis. Infection is more common in women than in men. Older women are more likely than younger women to have been infected with trichomoniasis.

### How do people get trichomoniasis?

The parasite passes from an infected person to an uninfected person during sex. In women, the most commonly infected part of the body is the lower genital tract (vulva, vagina, cervix, or urethra). In men, the most commonly infected body part is the inside of the penis (urethra). During sex, the parasite usually spreads from a penis to a vagina, or from a vagina to a penis. It can also spread from a vagina to another vagina. It is not common for the parasite to infect other body parts, like the hands, mouth, or anus. It is unclear why some people with the infection get symptoms while others do not. It probably depends on factors like a person’s age and overall health. Infected people without symptoms can still pass the infection on to others.

### What are the signs and symptoms of trichomoniasis?

About 70% of infected people do not have any signs or symptoms. When trichomoniasis does cause symptoms, they can range from mild irritation to severe inflammation. Some people with symptoms get them within 5 to 28 days after being infected. Others do not develop symptoms until much later. Symptoms can come and go.

Men with trichomoniasis may notice:

- Itching or irritation inside the penis;
- Burning after urination or ejaculation;
- Discharge from the penis.

Women with trichomoniasis may notice:

- Itching, burning, redness or soreness of the genitals;
- Discomfort with urination;
- A change in their vaginal discharge (i.e., thin discharge or increased volume) that can be clear, white, yellowish, or greenish with an unusual fishy smell.

Having trichomoniasis can make it feel unpleasant to have sex. Without treatment, the infection can last for months or even years.

## **What are the complications of trichomoniasis?**

Trichomoniasis can increase the risk of getting or spreading other sexually transmitted infections. For example, trichomoniasis can cause genital inflammation that makes it easier to get infected with HIV, or to pass the HIV virus on to a sex partner.

## **How does trichomoniasis affect a pregnant woman and her baby?**

Pregnant women with trichomoniasis are more likely to have their babies too early (preterm delivery). Also, babies born to infected mothers are more likely to have a low birth weight (less than 5.5 pounds).

## **How is trichomoniasis diagnosed?**

It is not possible to diagnose trichomoniasis based on symptoms alone. For both men and women, your health care provider can examine you and get a laboratory test to diagnose trichomoniasis.

## **What is the treatment for trichomoniasis?**

Trichomoniasis can be treated with medication (either metronidazole or tinidazole). These pills are taken by mouth. It is safe for pregnant women to take this medication. It is not recommended to drink alcohol within 24 hours after taking this medication.

People who have been treated for trichomoniasis can get it again. About 1 in 5 people get infected again within 3 months after receiving treatment. To avoid getting reinfected, make sure that all of your sex partners get treated. Also, wait 7-10 days after you and your partner have been treated to have sex again. Get checked again if your symptoms come back.

## **How can trichomoniasis be prevented?**

The only way to avoid STDs is to not have vaginal, anal, or oral sex.

If you are sexually active, you can do the following things to lower your chances of getting trichomoniasis:

- Be in a long-term mutually monogamous relationship with a partner who has been tested and has negative STD test results;
- Use latex condoms the right way every time you have sex. This can lower your chances of getting trichomoniasis. But the parasite can infect areas that are not covered by a condom - so condoms may not fully protect you from getting trichomoniasis.

Another approach is to talk about the potential risk of STDs before you have sex with a new partner. That way you can make informed choices about the level of risk you are comfortable taking with your sex life.

If you or someone you know has questions about trichomoniasis or any other STD, talk to a health care provider.

## **Where can I get more information?**

Division of STD Prevention (DSTD)  
Centers for Disease Control and Prevention  
[www.cdc.gov/std](http://www.cdc.gov/std)

CDC-INFO Contact Center  
1-800-CDC-INFO  
(1-800-232-4636)  
<https://www.cdc.gov/dcs/ContactUs/Form>

CDC National Prevention Information Network (NPIN)  
<https://npin.cdc.gov/disease/stds>  
P.O. Box 6003  
Rockville, MD 20849-6003  
E-mail: [npin-info@cdc.gov](mailto:npin-info@cdc.gov)

American Sexual Health Association (ASHA)  
<http://www.ashasexualhealth.org/stdsstis/>  
P. O. Box 13827  
Research Triangle Park, NC  
27709-3827  
1-800-783-9877

# A practical approach to the diagnosis and management of chlamydia and gonorrhea

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The 2 most frequent reportable bacterial sexually transmitted infections (STIs) worldwide and in Canada are those caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.<sup>1,2</sup> Rates of both infections have been increasing over the last decade despite public health efforts aimed at prevention, testing and treatment. In 2019, 139 389 cases of chlamydia and 35 443 cases of gonorrhea were reported in Canada, an increase of 33.1% and 181.7%, respectively, since 2010.<sup>2</sup> These increases may reflect improved diagnostics, increased screening and contact tracing or a true increase in incidence.<sup>2</sup>

Sexually transmitted infections have a substantial impact on affected individuals and communities. *Chlamydia trachomatis* and *N. gonorrhoeae* are commonly implicated pathogens in pelvic inflammatory disease and, if untreated, can lead to infertility.<sup>3</sup> Infection with a bacterial STI is associated with increased risk of HIV acquisition or transmission.<sup>4</sup> Perinatal transmission of *C. trachomatis* and *N. gonorrhoeae* can lead to ophthalmia neonatorum in infants, among other pathologies.<sup>5</sup> Treatment has become more challenging, given the increase in antimicrobial resistance in gonorrhea.<sup>6</sup>

We summarize the management of chlamydia and gonorrhea in primary care as health care providers work collectively toward the goal of decreasing the frequency of these infections and reducing associated morbidity through appropriate treatment. We draw on evidence from clinical practice guidelines, systematic reviews and meta-analyses (Box 1).

## Box 1: Literature review

We conducted a targeted literature search of MEDLINE and Embase from inception to July 2022. Search terms included “*Chlamydia trachomatis*,” “*Neisseria gonorrhoeae*,” “sexually transmitted infection,” “STI,” “urethritis,” “cervicitis,” “pelvic inflammatory disease,” “proctitis,” “epididymitis,” “diagnosis,” “screening” and “treatment.” We limited the search to articles in English. Our targeted search focused on identifying clinical practice guidelines, systematic reviews and meta-analyses, although we did not place any formal restriction on article type. We selected relevant articles, and manually reviewed their references for additional articles.

## Key points

- The incidence of chlamydia and gonorrhea, 2 common sexually transmitted infections, is increasing.
- Annual asymptomatic screening for chlamydia and gonorrhea should be performed in all sexually active patients younger than 30 years, with more frequent screening for higher risk patients.
- Nucleic acid amplification testing for chlamydia and gonorrhea should be performed in both asymptomatic and symptomatic patients at sites of sexual exposure, guided by a careful sexual history.
- The treatment recommendations for chlamydia and gonorrhea are evolving and clinicians should follow local guidance.
- Antimicrobial resistance in gonorrhea is increasing; optimal treatment should be guided by principles of antimicrobial stewardship.

## Why is taking a good sexual history important?

Taking a sexual history is essential to comprehensive care in patients presenting with STI symptoms and in asymptomatic people to assess for STI risk, determine the need for screening, address concerns and provide sexual health education.

Patients have reported wanting their health care provider to inquire about sexual health, but many face considerable barriers to self-disclosure of their sexual history.<sup>7,8</sup> Stigma is often associated with STIs. Providers conducting a sexual history should do so in a nonjudgmental, patient-centred and trauma-informed manner.<sup>9</sup> Syndemics theory describes how disease interacts with social constructs, which can help conceptualize how a person’s unique social, cultural and health context influences how they access STI care.<sup>10</sup> Establishing the patient’s pronouns, sexual orientation and gender identity is necessary to create an environment of respect and trust. The components of a sexual history can be remembered by the 5 Ps: partners, practices, protection, past history and pregnancy (Table 1).<sup>11</sup>

**Table 1: Approach to taking a sexual history\***<sup>11</sup>

Area	Examples of questions
Partners	<ul style="list-style-type: none"> <li>• Are you currently having sex of any kind?</li> <li>• In the last 2 months, how many sexual partners have you had?</li> <li>• What is/are the genders of your sexual partners?</li> <li>• Do your partners have other sexual partners? What is/are their gender(s)?</li> </ul>
Practices	<ul style="list-style-type: none"> <li>• To offer the most appropriate testing, can you tell me more about what types of sex you have?</li> <li>• What parts of your body are involved when you have sex? <ul style="list-style-type: none"> <li>• Genital sex (penis in the vagina)</li> <li>• Anal sex (penis in the anus)</li> <li>• Oral sex (mouth on penis, vagina or anus)</li> </ul> </li> <li>• How do you meet your sexual partners?</li> <li>• Have you or any of your partners used drugs?</li> <li>• Have you ever exchanged sex to meet your needs (money, housing, food etc.)?</li> </ul>
Protection	<ul style="list-style-type: none"> <li>• Do you and your partner(s) discuss STI prevention?</li> <li>• If you use prevention, what methods do you use?</li> <li>• How often do you use these methods (never, sometimes, all of the time)?</li> <li>• Have you received the human papillomavirus (HPV), hepatitis B (HBV) or hepatitis A (HAV) vaccine?</li> <li>• Have you ever used or considered using HIV pre-exposure prophylaxis (PrEP)?</li> </ul>
Past history	<ul style="list-style-type: none"> <li>• Have you ever been tested for STIs?</li> <li>• Have you ever been diagnosed and/or treated for an STI in the past?</li> <li>• Have any of your current or former partners ever been diagnosed or treated for an STI?</li> </ul>
Pregnancy	<ul style="list-style-type: none"> <li>• How important is it to you to prevent pregnancy?</li> <li>• Are you or your partner using contraception or any form of birth control?</li> </ul>

Note: STI = sexually transmitted infection.

\*Based on information contained in Reno H, Park I, Workowski K, et al. *A guide to taking a sexual history*. Atlanta: Centers for Disease Control and Prevention; reviewed 2022. Available: <https://www.cdc.gov/std/treatment/SexualHistory.htm#>

## What are common clinical presentations?

Most chlamydia and gonorrhea infections cause no symptoms.<sup>12</sup> If symptoms develop, the incubation period for gonorrhea is 2–7 days, compared with 2–6 weeks for chlamydia.<sup>13</sup> Chlamydia and gonorrhea may have genital or extragenital symptoms, which are generally reflective of the site of infection. The clinical presentations of chlamydia and gonorrhea overlap, and they are usually clinically indistinguishable.

### Genital symptoms

Urethritis is the most common syndrome in patients with a penis who are symptomatic. It is characterized by dysuria, urethral pruritis and discharge. Most cases of infectious urethritis are caused by *C. trachomatis* and *N. gonorrhoeae* or both. However, in almost half of cases of nongonococcal urethritis, no specific organism is identified despite extensive microbiological investigation (Box 2).<sup>14</sup>

Patients can develop acute epididymitis from chlamydia or gonorrhea, which is characterized by unilateral, posterior testicular pain and swelling, often accompanied by symptoms of urethritis. Among men younger than 35 years, *C. trachomatis* and *N. gonorrhoeae* are the most common causative organisms, but among older men and men who engage in insertive anal

intercourse, causative agents can include enteric organisms like *Escherichia coli*.<sup>15</sup>

Although cervicitis is often asymptomatic, symptoms may occur and include abnormal vaginal discharge or intermenstrual bleeding.<sup>16</sup> Findings on physical examination include purulent endocervical discharge or sustained endocervical bleeding. Most cases of cervicitis have no identified cause. In as many as 25% of cases, *C. trachomatis* or *N. gonorrhoeae* is identified.<sup>17</sup> In around 15% of female patients, pelvic inflammatory disease can develop, characterized by abdominal or pelvic pain, dyspareunia or abnormal uterine bleeding, with findings of cervical motion or adnexal tenderness on physical examination.<sup>18</sup> Patients may have infertility as a consequence of pelvic inflammatory disease. An uncommon complication of pelvic inflammatory disease is Fitz-Hugh-Curtis syndrome, characterized by right upper quadrant pain related to inflammation of the liver capsule.<sup>17</sup>

### Extragenital symptoms

Proctitis caused by chlamydia or gonorrhea may present with tenesmus, anorectal pain, bleeding and mucopurulent discharge. These infections typically occur in patients who engage in receptive anal sex, but can also be transmitted from the vagina to the anal canal.<sup>19</sup> *Chlamydia trachomatis*

## Box 2: Infectious differential diagnosis of common clinical presentations of sexually transmitted infections

### Urethritis

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*
- *Trichomonas vaginalis*
- *Neisseria meningitidis*
- *Hemophilus spp.*
- Herpes simplex virus
- Adenovirus

### Cervicitis

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Trichomoniasis*
- Herpes simplex virus
- *Mycoplasma genitalium*
- Bacterial vaginosis

### Proctitis

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis* (including lymphogranuloma venereum serovars)
- Syphilis
- Herpes simplex virus
- Mpox virus

### Epididymitis

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- Enteric organisms (e.g., *Escherichia coli*)

and *N. gonorrhoeae* are the most commonly identified pathogens in cases of infectious proctitis.<sup>20</sup>

The lymphogranuloma venereum (LGV) serovars (L1, L2, L3) of *C. trachomatis* can cause invasive infections that preferentially affect lymphatic tissue. Lymphogranuloma venereum can present as small painless ulcers or painful hemorrhagic proctitis, with complications including anal fistulae and strictures.<sup>21</sup> In the last 2 decades, LGV has emerged as an important cause of proctitis among men who have sex with men (MSM) in North America and Europe.<sup>22</sup>

Oropharyngeal infections with gonorrhea are commonly asymptomatic, although patients can present with sore throat, pharyngeal exudate or cervical lymphadenitis.<sup>23</sup> Chlamydia is not an important cause of pharyngitis.<sup>24</sup>

Although uncommon, gonorrhea infection can cause bacteremia, leading to septic arthritis or disseminated gonococcal infection, with tenosynovitis, dermatitis or polyarthralgias.<sup>23</sup> Reactive arthritis — characterized by polyarthritis, conjunctivitis or uveitis, and urethritis or cervicitis — can occur after an infection with chlamydia or gonorrhea, although chlamydia is the more common inciting infection.<sup>25</sup>

## Who should be screened for infection?

Opportunistic screening is critical in identifying asymptomatic chlamydia and gonorrhea infections. The Canadian Task Force on Preventive Health Care recommends annual opportunistic screening for chlamydia and gonorrhea in all sexually active people younger than 30 years.<sup>26</sup> Although based on low-quality evidence, an opportunistic approach to screening is likely to increase the number of STIs diagnosed and destigmatize sexual health conversations.

More frequent screening should be offered to people at higher risk of acquiring STIs, although little evidence exists to guide the optimal frequency of screening. Among MSM, current guidance suggests, at minimum, anatomic site-based screening for chlamydia and gonorrhea annually.<sup>13,24</sup> More frequent screening (i.e., every 3–6 months) is recommended for at-risk people of any gender within groups who may be disproportionately affected by STIs, including those taking HIV pre-exposure prophylaxis (PrEP), those who have recently had an STI, those living with HIV or those with multiple sexual partners.<sup>13,24,27</sup> One cohort study of 557 MSM and transgender women taking HIV PrEP found that semiannual STI screening would have led to delayed diagnosis in more than 30% of patients with chlamydia or gonorrhea, compared with quarterly screening.<sup>28</sup> Pregnant patients should be screened at their first prenatal visit, with rescreening in the third trimester if they initially test positive for or are at ongoing risk of STIs.<sup>13,24</sup>

Clinicians should determine appropriate anatomic sites for screening based on information from the sexual history, although they should consider screening extragenital sites (i.e., rectum and oropharynx), even in the absence of either reported symptoms or sexual exposures. Studies of people attending STI clinics have found that a considerable proportion of STIs are missed when STI testing is conducted only for patients with reported symptoms or on sites with known exposure, or when testing includes only urine.<sup>29,30</sup> Testing for gender-diverse patients will depend on their specific anatomy.

## How should patients be tested?

In asymptomatic patients, approaches to sample collection for nucleic acid amplification testing (NAAT) for chlamydia and gonorrhea include a first-void urine (first 10–20 mL, any time of day, at least 1 hour since previous void) or vaginal swab; other options include a urethral or cervical swab (Table 2). In patients with a vagina, a vaginal swab is preferred over first-void urine, as urine testing may detect 10% fewer infections.<sup>31</sup> Those with a neovagina or gender-affirming penile reconstruction should provide a urine sample for NAAT. Exogenous testing options include a pharyngeal or rectal swab for chlamydia and gonorrhea NAAT. In symptomatic patients, first-void urine and swabs of sites of reported symptoms should be collected for chlamydia and gonorrhea NAAT, and for gonorrhea culture and sensitivity testing. Patient-collected swabs are acceptable, as studies have shown equivalence between self- and clinician-collected oral, vaginal and rectal swabs for chlamydia and gonorrhea.

**Table 2: Testing for chlamydia and gonorrhea**

Site	Approach for asymptomatic patients or screening	Approach for symptomatic patients
Penile urethra	<ul style="list-style-type: none"> <li>First-void urine for NAAT for chlamydia and gonorrhea</li> </ul>	<ul style="list-style-type: none"> <li>Urethral swab for gonorrhea culture and sensitivity testing, and first-void urine for NAAT for chlamydia and gonorrhea</li> </ul>
Cervix or vagina*	<ul style="list-style-type: none"> <li>Vaginal swab (preferred), cervical swab or first-void urine for NAAT for chlamydia and gonorrhea</li> </ul>	<ul style="list-style-type: none"> <li>Cervical swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea, or</li> <li>Vaginal swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea, or</li> <li>First-void urine for NAAT for chlamydia and gonorrhea</li> </ul>
Throat	<ul style="list-style-type: none"> <li>Throat swab for NAAT for chlamydia and gonorrhea</li> </ul>	<ul style="list-style-type: none"> <li>Throat swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea</li> </ul>
Rectum	<ul style="list-style-type: none"> <li>Rectal swab for NAAT for chlamydia and gonorrhea</li> </ul>	<ul style="list-style-type: none"> <li>Rectal swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea</li> </ul>

Note: NAAT = nucleic acid amplification test.

\*For patients with a neovagina, a first-void urine is the preferred screening test. In symptomatic patients, efforts should be made to conduct gonorrhea culture and sensitivity testing, as well as NAAT for chlamydia and gonorrhea. When culture and sensitivity testing is not possible, either a cervical or vaginal swab for NAAT or a first-void urine is appropriate.

testing.<sup>32,33</sup> Self-collection may also improve uptake of STI screening.<sup>13,24</sup>

Clinicians should refer to their local microbiology laboratories for recommendations on collection and transport protocols in their region. First-void urine can be collected in a sterile urine container for chlamydia and gonorrhea NAAT. The swabs contained within chlamydia and gonorrhea NAAT kits can be used on the cervix, urethra, vagina, throat or rectum; swabs from these sites can also be sent for gonorrhea culture. Bacterial culture for chlamydia is not routinely performed in Canada.<sup>13</sup>

Genotyping of LGV serovars can be requested if a patient presents with a syndrome consistent with LGV.<sup>13</sup> Some Canadian jurisdictions will automatically test all positive rectal chlamydia swabs for LGV serovars. However, it is important to indicate suspicion for LGV on laboratory requisitions, as automatic LGV testing is not universal, and nonrectal specimens (e.g., genital ulcers) are not automatically tested.

## How should patients be treated?

### Gonorrhea

Treatment of gonorrhea is challenging, as it readily develops antimicrobial resistance, and guidelines are not congruent in their recommendations. The Canadian STI guideline recommends dual therapy with ceftriaxone or cefixime, plus azithromycin or doxycycline (Table 3).<sup>13</sup> The STI treatment guideline from the United States Centers for Disease Control and Prevention (CDC) increased the previously recommended ceftriaxone dose (Table 3).<sup>24</sup> The CDC also recommended against dual therapy based on increasing antimicrobial resistance, and concern for impacts on the microbiome and selective pressure on other pathogens.<sup>24</sup> It is likely that this approach will be adopted by guidelines from other jurisdictions in the future. If monotherapy with ceftriaxone is used, an increased dose of ceftriaxone is recommended, compared with that used in dual therapy

(Table 3).<sup>24</sup> Currently, given varying recommendations, clinicians should follow local guidance, which will be based on resistance patterns in their area.

### Chlamydia

The Canadian STI guideline recommends doxycycline or azithromycin as the first-line (preferred) treatment for chlamydia,<sup>13</sup> whereas the CDC recommends doxycycline as first-line treatment, with azithromycin as a second-line (alternate) regimen (Table 3).<sup>24</sup> The preference for doxycycline is based on a systematic review and meta-analysis comparing treatment with azithromycin and doxycycline for chlamydia, which found that treatment failed more often with azithromycin, particularly among men with rectal chlamydia.<sup>34,35</sup> Thus, doxycycline is the preferred agent for treating rectal chlamydia. If adherence to therapy is a concern, single-dose azithromycin may be preferred. For pregnant patients, azithromycin is the first-line treatment.<sup>13</sup> For patients with suspected or confirmed LGV, treatment with doxycycline should be continued for 21 days.<sup>13</sup>

### Other treatment considerations

Given the potential complexity of cases and the evolving treatment landscape, providers should consult with an expert in STI management when necessary. All patients being treated for chlamydia or gonorrhea should be strongly advised to abstain from sexual activity for 7 days after treatment and until all partners have been treated.<sup>13</sup> Sexual partners from the previous 60 days should be tested and treated, or offered expedited partner treatment (i.e., clinicians can provide empiric treatment for the patient to give to their partner), which has been found to reduce the rates of recurrent or persistent infection.<sup>36</sup> Details around indications and timing of tests of cure are discussed in Table 3. Tests of cure and repeat screening recommendations are often not followed, although they remain important for the appropriate care of the patient and to decrease transmission.<sup>37</sup>

**Table 3: Treatment of chlamydia and gonorrhea**

Pathogen	Canadian guideline <sup>13</sup>	CDC guideline <sup>24</sup>	Test of cure	Follow-up
<i>Chlamydia trachomatis</i>	<p><b>Preferred treatment</b></p> <ul style="list-style-type: none"> <li>Doxycycline (100 mg orally, twice daily for 7 d) or azithromycin (1 g orally, once)</li> <li>LGV: doxycycline (100 mg orally, twice daily for 21 d)</li> </ul> <p><b>Alternative treatment</b></p> <ul style="list-style-type: none"> <li>Levofloxacin (500 mg orally, daily for 7 d)</li> </ul> <p><b>Treatment for pregnant patients*</b></p> <ul style="list-style-type: none"> <li>Azithromycin (1 g orally, once)</li> </ul>	<p><b>First-line treatment</b></p> <ul style="list-style-type: none"> <li>Doxycycline (100 mg orally, twice daily for 7 d)</li> <li>LGV: doxycycline (100 mg orally, twice daily for 21 d)</li> </ul> <p><b>Second-line treatment</b></p> <ul style="list-style-type: none"> <li>Azithromycin (1 g orally, once) or levofloxacin (500 mg orally, daily for 7 d)</li> </ul> <p><b>Treatment for pregnant patients*</b></p> <ul style="list-style-type: none"> <li>Azithromycin (1 g orally, once) (preferred), or amoxicillin (500 mg orally, 3 times daily for 7 d)</li> </ul>	<p><b>Indications</b></p> <ul style="list-style-type: none"> <li>Suspected treatment failure</li> <li>Suspected poor adherence</li> <li>Nonpreferred regimen used</li> <li>Pregnancy</li> </ul> <p><b>Approach</b></p> <ul style="list-style-type: none"> <li>Swab for NAAT for chlamydia and gonorrhea 4 wk after therapy completed</li> </ul>	<ul style="list-style-type: none"> <li>Re-screen 3 mo after treatment completed</li> </ul>
<i>Neisseria gonorrhoeae</i>	<p><b>Preferred treatment</b></p> <ul style="list-style-type: none"> <li>Ceftriaxone (250 mg IM, once) and azithromycin (1 g orally, once), or</li> <li>Cefixime (800 mg orally, once) and azithromycin (1 g orally, once); this is considered an alternative regimen for pharyngeal infections and treatment of MSM</li> </ul> <p><b>Alternative treatment</b></p> <ul style="list-style-type: none"> <li>Ceftriaxone (250 mg IM, once) or cefixime (800 mg orally, once), and doxycycline (100 mg orally, twice daily for 7 d), or</li> <li>Azithromycin (2 g orally, once) and gentamicin (240 mg IM, once); this regimen should be considered only if severe allergy or documented resistance to cephalosporins</li> </ul> <p><b>Treatment for pregnant patients*</b></p> <ul style="list-style-type: none"> <li>Ceftriaxone (250 mg IM, once) or cefixime (800 mg orally, once), and azithromycin (1 g orally, once)</li> </ul>	<p><b>First-line treatment</b></p> <ul style="list-style-type: none"> <li>Ceftriaxone (500 mg IM, once, if patient weighs &lt; 150 kg; 1 g IM, once, if patient weighs &gt; 150 kg)</li> </ul> <p><b>Second-line treatment</b></p> <ul style="list-style-type: none"> <li>Cefixime (800 mg orally, once) or gentamicin (240 mg IM, once), and azithromycin (2 g orally, once)</li> </ul> <p><b>Treatment for pregnant patients*</b></p> <p>Same as above</p>	<p>Consider for all positive sites</p> <p><b>Indications</b></p> <ul style="list-style-type: none"> <li>Suspected treatment failure</li> <li>Suspected poor adherence</li> <li>Nonpreferred regimen used</li> <li>Pregnancy</li> <li>Pharyngeal infection</li> <li>Documented antimicrobial resistance</li> </ul> <p><b>Approach</b></p> <ul style="list-style-type: none"> <li>Swab for gonorrhea culture and sensitivity test 3–7 d after treatment (preferred) or swab for NAAT for chlamydia and gonorrhea 4 wk after treatment</li> </ul>	<ul style="list-style-type: none"> <li>Re-screen 3 mo after treatment completed</li> </ul>

Note: CDC = Centers for Disease Control and Prevention, IM = intramuscularly, MSM = men who have sex with men, NAAT = nucleic acid amplification test.

\*Doxycycline is contraindicated in pregnancy.

## What about antimicrobial resistance?

Globally and in Canada, rates of antimicrobial resistance in *N. gonorrhoeae* are increasing, with decreasing susceptibility to cephalosporins and azithromycin.<sup>6,38</sup> In Canada, between 2012 and 2016, the proportion of multidrug resistant *N. gonorrhoeae* increased from 6.2% to 8.9%, with most isolates identified in Ontario and Quebec.<sup>39</sup> Actions that clinicians can take to combat antimicrobial resistance are to perform gonorrhea culture and sensitivity testing when possible to limit

unnecessary antimicrobial use, and to forgo dual therapy for gonorrhea when chlamydia is excluded. Whether the widespread discontinuation of dual therapy for gonorrhea would negatively affect clinical outcomes or prevent antimicrobial resistance has not yet been established, however. Treatment can be delayed until test results are available in situations where reliable patient follow-up is likely. In cases of confirmed or suspected multidrug-resistant *N. gonorrhoeae*, clinicians should consider consulting an expert in the management of STIs.

## Conclusion

Chlamydia and gonorrhea are the most common bacterial STIs in Canada, and their incidence is increasing.<sup>2</sup> Most infections are asymptomatic, which highlights the importance of routine screening for people who are sexually active.<sup>26</sup> Screening and diagnostic testing in symptomatic patients should be guided by a comprehensive sexual health history, which also provides an opportunity for patient education around sexual health. However, the optimal screening frequency in different populations remains unclear. With increasing rates of antimicrobial resistance, treatment should be guided by adherence to the principles of antimicrobial stewardship.

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# Syphilis – CDC Fact Sheet



Syphilis is a sexually transmitted disease (STD) that can have very serious complications when left untreated, but it is simple to cure with the right treatment.

## What is syphilis?

Syphilis is a sexually transmitted infection that can cause serious health problems if it is not treated. Syphilis is divided into stages (primary, secondary, latent, and tertiary). There are different signs and symptoms associated with each stage.

## How is syphilis spread?

You can get syphilis by direct contact with a syphilis sore during vaginal, anal, or oral sex. You can find sores on or around the penis, vagina, or anus. You can also find them in the rectum, on the lips, or in the mouth. Syphilis can spread from an infected mother to her unborn baby.

## What does syphilis look like?

Syphilis is divided into stages (primary, secondary, latent, and tertiary), with different signs and symptoms associated with each stage. A person with **primary syphilis** generally has a sore or sores at the original site of infection. These sores usually occur on or around the genitals, around the anus or in the rectum, or in or around the mouth. These sores are usually (but not always) firm, round, and painless. Symptoms of **secondary syphilis** include skin rash, swollen lymph nodes, and fever. The signs and symptoms of primary and secondary syphilis can be mild, and they might not be noticed. During the **latent stage**, there are no signs or symptoms. **Tertiary syphilis** is associated with severe medical problems. A doctor can usually diagnose tertiary syphilis with the help of multiple tests. It can affect the heart, brain, and other organs of the body.

## How can I reduce my risk of getting syphilis?

The only way to avoid STDs is to not have vaginal, anal, or oral sex.

If you are sexually active, you can do the following things to lower your chances of getting syphilis:

- Being in a long-term mutually monogamous relationship with a partner who has been tested for syphilis and does not have syphilis;

- Using latex condoms, the right way, (<https://www.cdc.gov/condomeffectiveness/male-condom-use.html>) every time you have sex. Condoms prevent transmission of syphilis by preventing contact with a sore. Sometimes sores occur in areas not covered by a condom. Contact with these sores can still transmit syphilis.



Example of a primary syphilis sore.

## Am I at risk for syphilis?

Any sexually active person can get syphilis through unprotected vaginal, anal, or oral sex. Have an honest and open talk with your health care provider and ask whether you should be tested for syphilis or other STDs.

- All pregnant women should be tested for syphilis at their first prenatal visit.
- You should get tested regularly for syphilis if you are sexually active and
  - o are a man who has sex with men;
  - o are living with HIV; or
  - o have partner(s) who have tested positive for syphilis.

## I'm pregnant. How does syphilis affect my baby?

If you are pregnant and have syphilis, you can give the infection to your unborn baby. Having syphilis can lead to a low birth weight baby. It can also make it more likely you will deliver your baby too early or stillborn (a baby born dead). To protect your baby, **you should be tested for syphilis at least once during your pregnancy. Receive immediate treatment if you test positive.**

An infected baby may be born without signs or symptoms of disease. However, if not treated immediately, the baby may develop serious problems within a few weeks. Untreated babies can have health problems such as cataracts, deafness, or seizures, and can die.

## What are the signs and symptoms of syphilis?



Secondary rash from syphilis on palms of hands.

Symptoms of syphilis in adults vary by stage:

### *Primary Stage*

During the first (primary) stage of syphilis, you may notice a single sore or multiple sores. The sore is the location where syphilis entered your body. Sores are usually (but not always) firm, round, and painless. Because the sore is painless, it can easily go unnoticed. The sore usually lasts 3 to 6 weeks and heals regardless of whether or not you receive treatment. Even after the sore goes away, you must still receive treatment. This will stop your infection from moving to the secondary stage.



Secondary rash from syphilis on torso.

### *Secondary Stage*

During the secondary stage, you may have skin rashes and/or mucous membrane lesions. Mucous membrane lesions are sores in your mouth, vagina, or anus. This stage usually starts with a rash on one or more areas of your body. The rash can show up when your primary sore is healing or several weeks after the sore has healed. The rash can look like rough, red, or reddish brown spots on the palms of your hands and/or the bottoms of your feet. The rash usually won't itch and it is sometimes so faint that you won't notice it. Other symptoms you may have can include fever, swollen lymph glands, sore throat, patchy hair loss, headaches, weight loss, muscle aches, and fatigue (feeling very tired). The

~~ek\_bfa\_eXba~~ this stage will go away whether or not you receive treatment. Without the right treatment, your infection will move to the latent and possibly tertiary stages of syphilis.

### *Latent Stage*

The latent stage of syphilis is a period of time when there are no visible signs or symptoms of syphilis. If you do not receive treatment, you can continue to have syphilis in your body for years without any signs or symptoms.

### *Tertiary Stage*

Most people with untreated syphilis do not develop tertiary syphilis. However, when it does happen it can affect many different organ systems. These include the heart and blood vessels, and the brain and nervous system. Tertiary syphilis is very serious and would occur 10–30 years after your infection began. In tertiary syphilis, the disease damages your internal organs and can result in death.

### *Neurosypilis and Ocular Syphilis*

Without treatment, syphilis can spread to the brain and nervous system (neurosypilis) or to the eye (ocular syphilis). This can happen during any of the stages described above.

Symptoms of neurosyphilis include:

- severe headache;
- difficulty coordinating muscle movements;
- paralysis (not able to move certain parts of your body);
- numbness; and
- dementia (mental disorder).

Symptoms of ocular syphilis include changes in your vision and even blindness.

### **How will I or my doctor know if I have syphilis?**

Most of the time, a blood test is used to test for syphilis. Some health care providers will diagnose syphilis by testing fluid from a syphilis sore.

### **Can syphilis be cured?**

Yes, syphilis can be cured with the right antibiotics from your health care provider. However, treatment might not undo any damage that the infection has already done.

### **I've been treated. Can I get syphilis again?**

Having syphilis once does not protect you from getting it again. Even after you've been successfully treated, you can still be re-infected. Only laboratory tests can confirm whether you have syphilis. Follow-up testing by your health care provider is recommended to make sure that your treatment was successful.

It may not be obvious that a sex partner has syphilis because syphilis sores can be hidden in the vagina, anus, under the foreskin of the penis, or in the mouth. Unless you know that your sex partner(s) has been tested and treated, you may be at risk of getting syphilis again from an infected sex partner.

### **Where can I get more information?**

Syphilis and MSM - Fact Sheet

<https://www.cdc.gov/std/syphilis/stdfact-msm-syphilis.htm>

Congenital Syphilis - Fact Sheet

<https://www.cdc.gov/std/syphilis/stdfact-congenital-syphilis.htm>

STDs during Pregnancy - Fact Sheet

<https://www.cdc.gov/std/pregnancy/stdfact-pregnancy.htm>

### **STD information and referrals to STD Clinics**

CDC-INFO Contact Center

1-800-CDC-INFO (1-800-232-4636)

TTY: (888) 232-6348

Contact CDC-INFO

<https://www.cdc.gov/dcs/ContactUs/Form>



Darkfield micrograph of *Treponema pallidum*.

## Secnidazole for Trichomoniasis in Women and Men



Christina A. Muzny, MD, MSPH, and Olivia T. Van Gerwen, MD, MPH

### ABSTRACT

**Introduction:** Secnidazole (SEC), newly FDA-approved for trichomoniasis, is a potent 5-nitroimidazole with selective toxicity against various infections. It has been used internationally to treat trichomoniasis, bacterial vaginosis, and other infections for decades. Trichomoniasis is the most common non-viral sexually transmitted infection worldwide and is associated with significant morbidity. In comparison to the only other approved treatments for trichomoniasis in the U.S.—metronidazole and tinidazole—SEC has favorable pharmacokinetics, including a longer half-life, and a lower minimal lethal concentration against *Trichomonas vaginalis*.

**Objectives:** Provide an updated, comprehensive review of the literature evaluating SEC as a treatment for trichomoniasis in women and men.

**Methods:** We conducted a search to identify existing research on SEC and trichomoniasis. On August 6, 2021, we searched MEDLINE using the terms “secnidazole” and “trichomon.\*” We excluded reviews, editorials, case reports, and small case series.

**Results:** We identified 29 articles; 14 of which were included: 5 reported in vitro pharmacologic data on SEC, 6 were observational studies, and 4 were controlled clinical trials (1 observational study also reported in vitro pharmacologic data). Six studies reported data on women only, 1 on men only, and 3 on women and men. These studies showed that SEC—as a single dose or 3-day course—had comparable efficacy to multi-dose metronidazole for treating trichomoniasis in women and men, was generally well tolerated by patients, and had a favorable pharmacokinetic profile. A single 2-g dose of SEC also led to a microbiologic cure rate of 92.2% in the first randomized, double-blind, placebo-controlled study of trichomonas-infected US-based women.

**Conclusion:** SEC is an efficacious and safe treatment for women and men with trichomoniasis. Single-dose administration makes it a favorable treatment option for patients, especially in cases where adherence to other multi-dose treatment regimens could be problematic. **Christina A. Muzny and Olivia T. Van Gerwen. Secnidazole for Trichomoniasis in Women and Men. Sex Med Rev 2022;10:255–262.**

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**Key Words:** Trichomoniasis; *Trichomonas vaginalis*; Secnidazole; Metronidazole; Tinidazole; Sexually Transmitted Infections

### INTRODUCTION

Trichomoniasis is the most prevalent non-viral sexually transmitted infection (STI) worldwide.<sup>1</sup> Since it is not a reportable STI, reliable prevalence estimates are limited, but a recent population-based epidemiologic study found that 1.8% of women and 0.5% of men ages 18–59 were affected in the

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U.S.<sup>1–3</sup> Up to 85% of patients with trichomoniasis may be asymptomatic.<sup>1</sup> For symptomatic women, exam findings can include abnormal vaginal discharge, as well as vaginal and cervical inflammation.<sup>1</sup> The Centers for Disease Control and Prevention (CDC) recommends diagnostic testing for trichomoniasis for all women seeking care for vaginal discharge and annual screening for all women with human immunodeficiency virus (HIV), including those who are pregnant.<sup>1</sup> Screening might also be considered for women being screened for chlamydia and gonorrhea,<sup>4</sup> as well as asymptomatic women at high risk of infection (eg, multiple recent sexual partners, history of other STIs, drug use, or participation in commercial sex work).<sup>1</sup>

Trichomoniasis is associated with significant morbidity if not treated promptly and appropriately. In women, trichomoniasis

can cause vaginitis, cervicitis, and pelvic inflammatory disease.<sup>5–7</sup> It has also been associated with cervical cancer,<sup>8</sup> infertility,<sup>9,10</sup> and adverse birth outcomes such as preterm birth.<sup>11–15</sup> In men, trichomoniasis can result in non–gonococcal urethritis, epididymitis, prostatitis, and infertility.<sup>1,3,16,17</sup> Infection can increase the risk for HIV and other STIs (eg, chlamydia, gonorrhea, herpes simplex virus, and syphilis) in both sexes.<sup>5,18</sup> Co-infection of bacterial vaginosis (BV) and *Trichomonas vaginalis* is common, with rates of 60–80%.<sup>19</sup> However, despite its high prevalence, and significant clinical implications, trichomoniasis receives little attention in the public health sector.<sup>20–22</sup>

Secnidazole (SEC), Solosec (Lupin Pharmaceuticals) is a potent antimicrobial drug classified as a next-generation 5-nitroimidazole.<sup>23,24</sup> SEC is a structural analogue of metronidazole (MTZ) and tinidazole (TDZ)—the 2 5-nitroimidazoles most frequently recommended for treatment of *T. vaginalis*—that differs from these compounds in the nitrogen ring adjacent to the nitro group.<sup>1,23,25</sup> These minor distinctions are likely responsible for the unique functional characteristics of SEC compared to other 5-nitroimidazoles, since their antipathogenic activity is primarily a function of the nitro group.<sup>23</sup> SEC is selectively toxic against numerous anaerobic Gram-positive and Gram-negative bacteria and protozoa, which occurs due to passive diffusion into the pathogen, and subsequent activation through reduction of the 5-nitroimidazole group.<sup>23,25</sup>

SEC has been used internationally to treat various bacterial and parasitic infections since the late 1960s,<sup>26</sup> but was only recently FDA-approved to treat BV in the U.S.<sup>27,28</sup> Evidence to support SEC as an effective treatment for trichomoniasis dates back to 1976.<sup>29</sup> Several additional studies have since been conducted to evaluate its safety and efficacy against trichomoniasis, as well as its pertinent pharmacologic properties.<sup>23,26</sup> The purpose of this study was to conduct a review of the literature to summarize the data available on the use of SEC to treat trichomoniasis in women and men.

## METHODS

We conducted a literature review in August 2021 to identify all active clinical trials and all published, peer-reviewed original research on SEC for the treatment of trichomoniasis in women and men, including in vitro and in vivo studies. We used the search terms “secnidazole” and “trichomon\*” to identify active studies registered on clinicaltrials.gov and articles indexed in MEDLINE (PubMed) from 1946 to August 6, 2021. Articles were included if they described studies that evaluated the pharmacokinetic characteristics of SEC or the safety and/or efficacy of SEC as a treatment for trichomoniasis in women and men. Articles were excluded if they evaluated other 5-nitroimidazoles (ie, MTZ, TDZ) or if they were case reports; small case series; reviews; and commentaries, correspondence, or editorials. If deemed relevant, the title and abstract were reviewed to further validate the meeting of our inclusion and exclusion criteria; if a

determination could not be made from the abstract, full text review of the article was performed. Reference lists of all articles identified through the PubMed search were also reviewed to identify any additional articles that may have been pertinent to this topic. If it was unclear whether an article was appropriate for inclusion, the authors reviewed, and discussed the article further to decide whether to include it. Institutional Review Board approval of this study was not required as it is a review of the literature on SEC and trichomoniasis, and no human participants were enrolled.

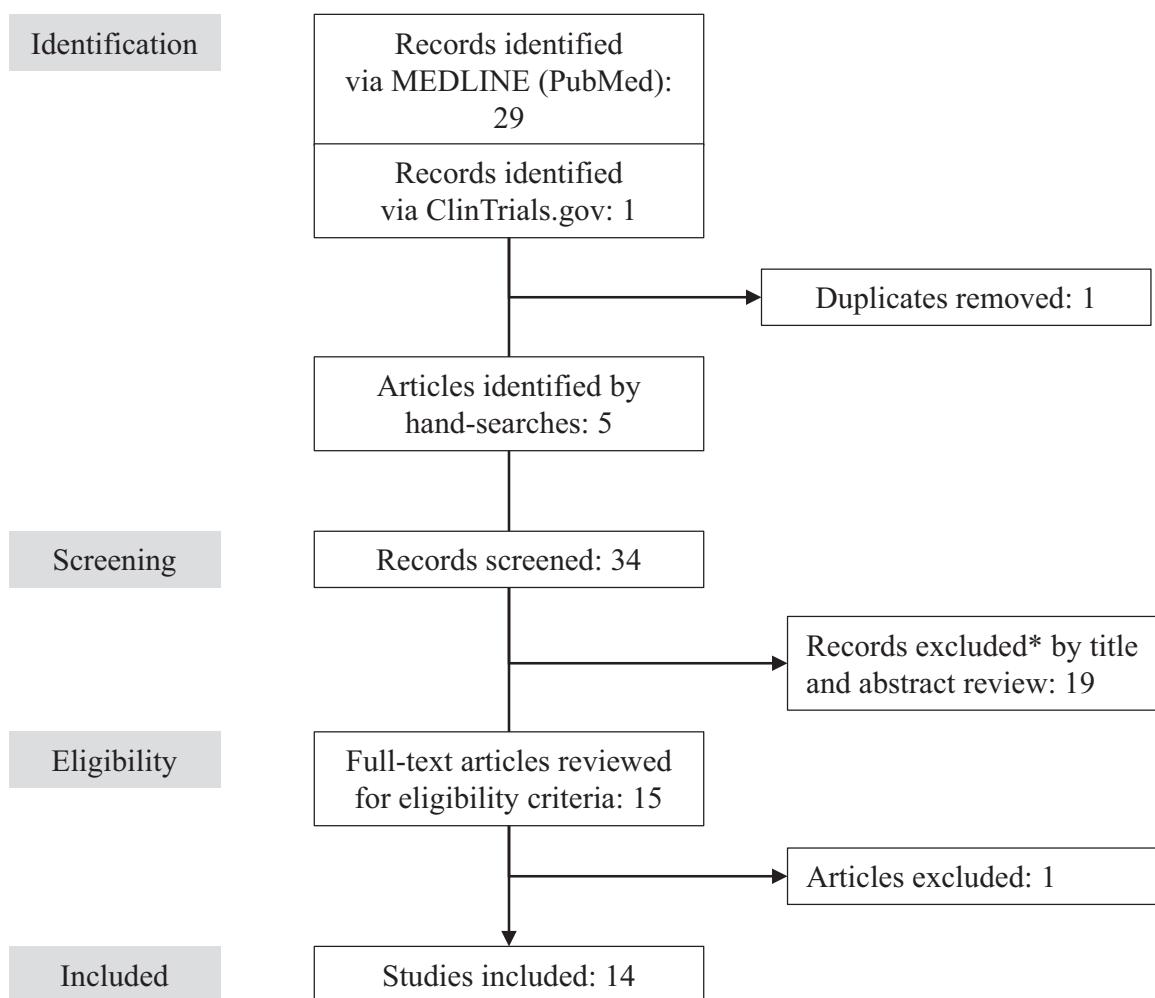
## RESULTS

Twenty-nine articles were identified through the PubMed search; all 29 were screened for eligibility according to the pre-specified inclusion/exclusion criteria (Figure 1). One study was identified on clinicaltrials.gov<sup>24</sup> and removed as a duplicate. Based on article titles and abstracts, 19 articles were excluded, leaving 10 articles<sup>24,29–37</sup> for full-text review. Based on hand-searches of the excluded review articles, 5 additional articles were identified,<sup>38–42</sup> for a total of 15 articles. One article, which did not have an abstract to review<sup>37</sup> was later excluded after full-text review of the study evaluated a combined treatment of SEC plus itraconazole for women with mixed cervical-vaginal infection. The final set of 14 articles were included in this review. Six of the 14 articles were non–English language studies translated from French, Ukrainian, Portuguese, and Spanish to English.<sup>30,38–42</sup> Five reported in vitro data characterizing the pharmacodynamic, and pharmacokinetic (PK) properties of SEC.<sup>29,31,34–36</sup> Nine articles reported in vivo data on the use of SEC for the treatment of trichomoniasis. Six were observational studies (3 in women, 3 in women and men); 4 were controlled clinical trials (3 in women, 1 in men only).<sup>24,29–36</sup> One observational study included both in vitro and in vivo data on SEC.<sup>36</sup> Most observational studies were published in the late 1970s, none were conducted in the U.S., and none were published in English.<sup>36,38–42</sup> Four placebo- or active-controlled clinical trials evaluated the efficacy and safety of SEC for the treatment of *T. vaginalis* in men,<sup>33</sup> women,<sup>24</sup> and both men and women.<sup>30,32</sup>

### In-Vitro Studies

In vitro and PK studies have shown that the half-life of SEC ranges from 17–19 hours,<sup>29,34,36,43</sup> which is considerably longer than other 5-nitroimidazoles, including MTZ (ie, 7–8 h)<sup>36</sup> and TDZ (ie, 12–13 h).<sup>29,34,36</sup> These studies also demonstrated that the half-life of SEC is longer in men vs women (20 vs 14 h).<sup>34,36,38</sup> Other PK data showed no clinically meaningful differences in SEC exposure (maximum serum concentration and area under the curve) between men and women.<sup>34,36</sup>

The antimicrobial activity of SEC was found to be similar to that of other drugs in the 5-nitroimidazole class. In general, SEC and MTZ have equipotent activity against *T. vaginalis* according to minimal inhibitory concentration (MIC) and minimal



**Figure 1.** Flow chart. \*Exclusion criteria: case reports; small case series; reviews; and commentary, correspondence, editorials. BV, bacterial vaginosis; STIs, sexually transmitted infections; TV, *Trichomonas vaginalis*.

trichomonacidal concentration (MTC) levels, 2 measurements that represent the lowest amount of a compound needed to inhibit bacterial or trichomoniasis growth, respectively.<sup>35,36</sup> The minimal lethal concentration (MLC) of SEC was found to be 56% lower than that of MTZ against *T. vaginalis* in one study, which may indicate that SEC is more toxic toward this pathogen.<sup>31,44</sup>

### Observational Studies

A series of 6 observational studies of SEC for *T. vaginalis* was published in the late 1970s; none were conducted in the U.S. or published in English.<sup>36,38-42</sup> Overall, in patients with *T. vaginalis*, a single dose of 2-g oral SEC resulted in cure rates—microbiologic, symptomatic, or both—ranging from 94–100% (*Table 1*). Cure rates were assessed with wet mount microscopy in 3 studies<sup>40-42</sup>; wet mount and culture in 2 studies<sup>36,38</sup>; and wet mount, culture, and molecular testing (ie, nucleic acid amplification tests [NAATs]) in one study.<sup>39</sup> One study evaluated patients with both acute (n = 21) and persistent trichomoniasis (n = 46), with the acute group receiving a single 2-g oral dose of

SEC and the chronic group receiving 3, 2-g oral doses of SEC every other day.<sup>39</sup> Results were not separated by treatment arm, but the overall microbiologic and symptomatic cure rate for both groups combined was 97% (n = 65). Patients were also highly compliant with SEC treatment and SEC was found to be generally well-tolerated, with a low rate of adverse events.<sup>39</sup>

### Randomized Controlled Trials

*Table 2* summarizes the randomized controlled trials that have been conducted to evaluate the efficacy and safety of SEC for the treatment of *T. vaginalis* in women and men.

In a controlled clinical trial of MTZ vs SEC, 60 women (ages 18–50 years) were randomly assigned to 3 treatment groups in which one of the following study drugs was administered intravaginally as ovules: MTZ 500 mg daily for 10 days, SEC 500 mg daily for 3 days, and SEC 500 mg daily for 7 days.<sup>30</sup> At the end of treatment, all women in all groups had microbiologic cure based on wet mount microscopy. Among patients who received MTZ, clinical remission occurred within a mean (standard deviation [SD]) of 4.2 (1.4) days, and symptoms were significantly

**Table 1.** Observational trials of SEC for *T. vaginalis*

First author, y (country)	Treatment	M/F	Cure rate	AEs
Piato, 1977 <sup>41</sup> (Brazil)	SEC 2-g oral SD	0/50	94%*	Nausea and vomiting: 4.0% Nausea: 4.0% Nausea and dizziness: 2.0% Bitter taste: 2.0% Edema (eyelid, vulva): 2.0%
Rocha, 1977 <sup>42</sup> (Brazil)	SEC 2-g oral SD	0/50	100%* 96%†	Transient epigastralgia: 2.0%
Siboulet, 1977 <sup>38</sup> (France)	SEC 2-g oral SD	76/104	95.5%*	Nausea/gastralgia: 8.8% Gastric burning: 1.1%
Bravo, 1978 <sup>40</sup> (Brazil)	SEC 500-mg q12 h × 4 d SEC 2-g oral SD	0/48 0/49	97.9%† 100%†	Mild GI effects: 4.1% Bad taste, thirst, dizziness: 3.1% Bad taste, pyrosis: 1.0%
Videau, 1978 <sup>36</sup> (France)	SEC 2-g oral SD	56/84	97.1%†	Nausea: 4%
Dyudyun, 2016 <sup>39</sup> (Ukraine)	SEC 2-g oral SD <sup>§</sup> SEC 2-g oral MD (3 d) <sup>¶</sup>	34/33	97.0%†	Dyspepsia: 4.5% Metallic taste: 3.0%

AE = adverse event; BID = twice daily; d = days; F = females; GI = gastrointestinal; M = males; MD = multiple doses; SD = single dose; SEC = secnidazole.

\*Microbiologic cure (wet mount: Piato, Rocha, Bravo; wet mount and culture: Siboulet, Videau; wet mount, culture, and molecular: Dyudyun).

†Microbiologic and symptomatic cure.

‡Symptomatic cure

§Treatment for patients experiencing their first occurrence of *T. vaginalis*.

¶Treatment for patients with persistent trichomoniasis.

reduced in 70% of patients. Among those who received SEC for 3 days, clinical remission occurred within a mean (SD) of 7.0 (2.0) days, and symptoms were significantly reduced in 75% of patients. Among those who received SEC for 7 days, clinical remission occurred within a mean (SD) of 4.0 (1.0) days, and symptoms were significantly reduced in 90% of patients.<sup>30</sup>

In a controlled clinical trial of *Mentha crispa* vs SEC, 60 women (ages ≥18 years) with *T. vaginalis* were randomly assigned to *M. crispa* 24 mg (2 oral tablets of 12 mg) or SEC 2 g by mouth as a single dose.<sup>32</sup> *M. crispa* (Lamiaceae) is a species of

garden mint with traditional medicinal properties that is administered as a dry extract of its stems and leaves.<sup>32,45</sup> After 7 days, microbiologic cure rates were 90% in the *M. crispa* group, and 97% in the SEC group.<sup>32</sup> There were no significant between-group differences in the absence or presence of signs and symptoms.<sup>32</sup>

In another study, 85 men diagnosed with trichomoniasis underwent treatment with either SEC, ornidazole, or MTZ.<sup>33</sup> In the SEC group, male patients (n = 30) and their partners were each administered a single 2-g dose of SEC by mouth and

**Table 2.** Controlled clinical trials of SEC for *T. vaginalis*

First author, y (country)	Treatment	M/F	Cure rate	AEs
Özbilgin, 1994 <sup>33</sup> (Turkey)	SEC 2-g oral SD MTZ 250-mg oral TID (7 d) ORZ 500-g BID oral (5 d)	30/0 29/0 26/0	100% 100% 100%	NR
Buitron Garcia Figueroa, 1997 <sup>30</sup> (Mexico)	MTZ 500-mg ovules QD (10 d) SEC 500-mg ovules QD (3 d) SEC 500-mg ovules QD (7 d)	0/20 0/20 0/20	70%, 75%, 90%	0%, 0%, 0%
Moraes, 2012 <sup>32</sup> (Brazil)	<i>M. crispa</i> 24-mg oral SD SEC 2-g oral SD	0/30 0/30	90.0% 96.6%	20.0% (unpleasant taste [6.6%), nausea [3.3%], headache [3.3%], epigastric pain [3.3%], vomiting [3.3%]), 70.0% (metallic taste [50.0%], nausea [16.6%], unpleasant odor in urine [3.3%])
Muzny, 2021 <sup>24</sup>	SEC 2-g oral SD Placebo oral SD	0/147	92.2%, 1.5%	14.9% (≥3%: nausea [2.7%], vulvovaginal candidiasis [2.7%]), 22% (≥3%: headache [6.8%], nausea [4.1%], vomiting [2.7%], trichomoniasis [2.7%])

AE = any adverse event; BID = twice daily; d = days; F = females; M = males; MTZ = metronidazole; NR = not reported; ORZ = ornidazole; SD = single dose; SEC = secnidazole; TID = three times daily.

evaluated 5 days later.<sup>33</sup> At this 5-day follow-up, all patients who received SEC experienced a symptomatic and microbiologic cure.<sup>33</sup>

Most recently, the first randomized, double-blind, placebo-controlled, delayed-treatment study in the U.S. evaluating the efficacy and safety of a single 2-g dose of oral SEC in 147 women with trichomoniasis was conducted.<sup>24</sup> At the test-of-cure (TOC) visit 6–12 days after initial randomization, the microbiologic cure rate was 92.2% (95% CI: 82.7–97.4) in the SEC group and 1.5% (95% CI: 0.0–8.0) in the placebo group ( $P < 0.001$ ).<sup>24</sup> For women who received placebo at the baseline visit, the opposite treatment was given at the TOC visit to ensure all participants were treated per standard of care. Subgroup analyses of women with HIV, BV, or vaginal symptoms at baseline showed cure rates of 100%, 92.9%, and 95.2%, respectively, after treatment with SEC.<sup>24</sup> No matching patients in the placebo group had a negative *T. vaginalis* culture at TOC (all  $P < 0.001$ ).<sup>24</sup> SEC was generally well tolerated. The most frequent adverse events were vulvovaginal candidiasis and nausea (each 2.7%) and no serious adverse events were observed.

## DISCUSSION

In reviewing data on SEC for the treatment of trichomoniasis, we found the efficacy of SEC, given as a single oral dose or a 3-day course, was comparable to multi-dose MTZ or a single dose of *Mentha crispa*. MTZ was approved in the early 1960s to treat trichomoniasis and is the current standard of care.<sup>46</sup> Only one study has been conducted on *Mentha crispa* for the treatment of trichomoniasis, and it is not currently a recommended or routinely used treatment in the U.S. Cure rates for SEC—symptomatic cure, microbiologic, and both—were high for all studies, with rates following single-dose regimens ranging from 92.2–100%. Overall, SEC had a favorable safety profile, as the occurrence of individual adverse events was  $\leq 10\%$  in all but one study<sup>32</sup> (50.0% metallic taste and 16.7% nausea). SEC also has potentially advantageous PK attributes, including a substantially longer half-life than other 5-nitroimidazoles, as well as lower MLC and similar MIC and MTC compared to MTZ.

Based in part on the supportive findings of the aforementioned 2021 U.S. randomized trial,<sup>24</sup> SEC was approved by the FDA for the treatment for adults with trichomoniasis as a single 2-g oral dose on June 30, 2021.<sup>44,47</sup> SEC has also been an FDA-approved treatment for women with BV since 2017, and the new supplemental indication makes SEC the only single-dose oral medication on the market for both trichomoniasis, and BV.<sup>24,47</sup>

For the treatment of trichomoniasis, the 2020 American College of Obstetricians and Gynecologists (ACOG) Clinical Management Guidelines and 2021 CDC STI Treatment Guidelines now recommend MTZ 500 mg orally twice daily for 7 days in all *T. vaginalis*-infected women, or alternatively, TDZ oral 2-g single dose.<sup>1,5</sup> In men, the CDC recommends MTZ 2-g single

dose or alternatively, TDZ oral 2-g single dose.<sup>1</sup> However, it must be noted that both sets of updated guidelines were released before our study<sup>24</sup> was published, and prior to SEC being FDA-approved for treatment of trichomoniasis.

Therefore, although SEC is not currently included in the 2021 CDC STI Treatment Guidelines or ACOG 2020 Guidelines for trichomoniasis, we believe the findings of this review demonstrate that it could represent an additional treatment option to those currently recommended for trichomoniasis. In the limited comparative data identified in this review SEC performed as good as or better than multi-dose MTZ in curing trichomoniasis, and both drugs were similarly well tolerated by patients. However, there are no studies directly comparing SEC to multi-dose MTZ, which is an important area of future research. It should be noted that the studies used to support the guideline changes and evaluate the MTZ 2-g dose vs MTZ 500 mg BID 7-day dose were not blinded to patient or investigator.<sup>48</sup> The SEC trial,<sup>24</sup> although against placebo, was double-blinded, multi-center, and had similar demographics. In terms of tolerability, in the MTZ trial, 33% (multi-dose group) and 34% (single-dose group) of patients experienced  $\geq 1$  adverse events,<sup>48</sup> while only 15% of patients experienced  $\geq 1$  adverse events in our recent trial on SEC.<sup>24</sup>

Current guidelines recommend that choice of treatment be based on patient preference, cost, convenience, adherence, and ease of use. As the cost of SEC and other 5-nitroimidazoles varies by region and individual patient and are based upon state Medicaid, insurance coverage, and patient assistance eligibility, the choice of treatment option for trichomoniasis should be weighed against other important mitigating factors. In evaluating cost, it is also appropriate to consider the overall societal cost related to non-adherence to multi-dose therapies for trichomoniasis. Such societal cost burdens include increased visits due to recurrent *T. vaginalis* infection as well as increased costs related to acquisition and treatment of more significant and lifelong disease, including HIV acquisition/transmission as well as other STI acquisition. Finally, there are broader general psychosexual burdens that make adherence with a single dose option beneficial. Another benefit of oral SEC is that it is the only single-dose medication that is also FDA-approved for concurrent BV treatment. SEC is administered as a single 2-g oral dose for trichomoniasis, which also may lead to favorable adherence rates in both patients and their partners. Poor treatment compliance is recognized as a potential cause of early repeat *T. vaginalis* infections, and duration of therapy can be a barrier that adversely affects adherence.<sup>49,50</sup> Research has shown that adherence to multi-dose antibiotics is low—with one study reporting rates of only 50–63% for patients taking multidose MTZ for BV<sup>51,52</sup>—and compliance can worsen as the length of therapy increases.<sup>53</sup> Although no research has yet been conducted to demonstrate that single-dose drug regimens are superior to multi-dose regimens for trichomoniasis, the single-dose administration of SEC could potentially improve patient adherence, and thus reduce

the partner-to-partner cycle of reinfections in this population, thereby improving overall outcomes.<sup>28,49</sup> Additionally, single-dose therapies may help control the spread of trichomoniasis in countries where prevalence of trichomoniasis is high.

## CONCLUSION

As the recommended treatment for trichomoniasis in all women has moved to the multi-dose MTZ regimen, patient adherence could become a potential issue.<sup>54</sup> Single-dose treatment options are convenient and likely to improve patient adherence, especially in populations at risk for non-adherence.<sup>49</sup> SEC is a newly approved treatment for trichomoniasis in women and men that was found to have comparable efficacy to prolonged MTZ and a favorable safety profile in our review.

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**Conflict of Interest:** Christina A. Muzny has received research grant support from Lupin Pharmaceuticals, Inc, Abbott Molecular, and Gilead Sciences, Inc; serves as a consultant for the Centers for Diseases Control and Prevention, Lupin Pharmaceuticals, Inc, and BioFire Diagnostics; receives honoraria from Elsevier, Abbott Molecular, Cepheid, Becton Dickinson, Roche Diagnostics, and Lupin Pharmaceuticals, Inc. Olivia T. Van. Gerwen has received research grant support from Gilead Sciences, Inc, and Abbott Molecular.

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## STATEMENT OF AUTHORSHIP

Christina A. Muzny: Conception and Design, Acquisition of Data, Analysis and Interpretation of Data, Drafting the Article, Revising it for Intellectual Content, Final Approval of the Completed Article; Olivia T. Van Gerwen: Conception and Design, Acquisition of Data, Analysis and Interpretation of Data, Drafting the Article, Revising it for Intellectual Content, Final Approval of the Completed Article.

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# Why risk matters for STI control: who are those at greatest risk and how are they identified?

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## ABSTRACT

Identifying groups most at risk of sexually transmissible infections (STIs) is important for prioritising screening, targeting prevention strategies and alleviating the burden of STIs. However, identifying those at risk of STIs is complicated by stigma associated with STIs, undisclosed risk behaviour, and the fact that STI epidemics are diversifying beyond traditional risk groups typically characterised by demographics and sexual behaviours alone. In this review, we describe the epidemiology of STIs among traditional and emerging risk groups, particularly in the context of uptake of HIV pre-exposure prophylaxis (PrEP), increasing STI transmission among heterosexual people, and the concentration of STI burden among specific subgroups not readily identifiable by health services. Risk diversification poses significant challenges, not only for risk-based testing, but also for the costs and resources required to reach a broader range of constituents with preventive and health promotion interventions. As drivers of STI risk are not purely behavioural, but relate to relative STI prevalence within sexual networks and access to sexual health care and testing, localised surveillance and research is important in ensuring risk is appropriately understood and addressed within local contexts. Here, we review the evidence on the benefits and harms of risk-guided versus population-based screening for STIs among key populations, discuss the importance of risk-guided interventions in the control of STIs, and explore contemporary approaches to risk determination.

**Keywords:** chlamydia, gonorrhoea, risk assessment, risk populations, screening, sexual health, STIs, syphilis.

## Introduction

There are an estimated 374 million new infections of curable sexually transmissible infections (STIs), such as chlamydia, gonorrhoea, syphilis and trichomoniasis, annually.<sup>1</sup> If left untreated, these infections can lead to serious sequelae, including pelvic inflammatory disease (PID), infertility, increased risk of HIV acquisition and, in pregnancy, neonatal death. With the majority of acute bacterial STIs being asymptomatic, identifying groups most at risk of infection is important for prioritising screening, targeting prevention strategies and alleviating the burden of STIs. Not adequately identifying people at high risk of STIs can limit the effectiveness of preventive interventions and lead to unnecessary testing and health-systems costs. Identifying those at risk of STIs risk is also complicated by the stigma associated with STIs and associated behaviours that limit individuals' disclosure of information about risk practices. Risk-based STI testing guidelines have traditionally centred on grouping people according to demographics and behaviours that have been identified in research and clinical practice as being associated with greater likelihood of STI diagnosis. However, the periodic emergence of STI epidemics among non-traditional risk populations, and the clustering of STIs in behaviourally specific subgroups within traditional risk populations, complicates the delivery of preventive interventions and care.

In this review, we describe the epidemiology of STIs among traditional and emerging risk groups, and explore contemporary approaches to risk determination. We review the evidence on the benefits and harms of risk-guided versus population-based screening for

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STIs among key populations, describe novel methods to identify risk, and discuss the importance of risk-guided interventions in the control of STIs.

## Traditional and emerging risk populations

The burden of STIs has historically been concentrated among what are typically referred to as 'key populations'. The World Health Organization's (WHO) global health sector strategy on STIs suggests that each country needs to 'define the specific populations that are most affected by STI epidemics' and that their response should be 'based on epidemiological and social context'.<sup>1</sup> These key populations are broadly categorised based on demographics such as gender and age, and specific sexual behaviours, such as number and gender of sexual partners. Specific populations that are highlighted in WHO guidance include adolescents and young people, men who have sex with men (MSM), transgender people, sex workers, and people who use drugs.

### Adolescents

Although young people and adolescents have been long recognised as a priority population for STIs,<sup>2</sup> targeted approaches are challenged by the fact they represent a substantial percentage of the general population and a behaviourally heterogeneous group. An analysis of data from the Global Burden of Diseases study found that adolescents have a higher STI burden than other age groups, and although overall the age-standardised incidence rate of STIs is trending down globally, the actual number of incident infections is increasing, likely due to the growth in the sexually active population and an increasing number of infections in adolescents.<sup>3</sup> Although there are biological factors which increase risk (e.g. young females can be more susceptible to chlamydia and HPV due to lower production of cervical mucus and increased cervical ectopy<sup>4</sup>), key drivers of risk among young people and adolescents include simultaneously being more likely to engage in sexual risk behaviour (e.g. concurrent partners and condomless sex)<sup>5</sup> and less likely to access sexual health services.<sup>5</sup> Low rates of seeking sexual health care among adolescents are likely, in part, to be associated with concerns about confidentiality and discomfort in discussing sexual health concerns, as well as lack of knowledge about available services.<sup>6</sup> Typically lower rates of general health-seeking behaviours among males drive lower rates of STI screening in general practice,<sup>7</sup> with testing among heterosexual males more likely to be driven by symptomatic presentation or partner notification.<sup>8</sup>

Trends in STI diagnoses among young people are dynamic and fluctuate across many settings. A recent analysis of data from the US found that among the youngest group, those aged 12–17 years, chlamydia and gonorrhoea positivity decreased, whereas it increased for the other age groups.<sup>9</sup>

Insights garnered from behavioural epidemiology data can be used to understand such changes and also guide priorities for risk-based screening and other interventions. In this study, the authors suggest decreasing positivity among those aged 12–17 years may be associated with a declining proportion of high school students who report ever having sex, having fallen from 47.4% in 2011 to 39.5% in 2017.<sup>10</sup> In contrast, repeated behavioural surveillance of high school students in Australia found the proportion of students reporting ever having penetrative sex increased from 34.7% in 2002 to 46.6% in 2018.<sup>11</sup> As routine presentation to primary care remains the main access point to the healthcare system for many young people, opportunistic STI screening relies on clinicians being comfortable asking young people about sex and sexual risk, and creating 'safe' clinical environments where young people feel comfortable discussing and disclosing information about sexual practices.

### Heterosexuals

Although MSM in high-income countries carry a significant burden of STIs, there is evidence that prevalence of STIs is increasing among heterosexual populations. For example, although gonorrhoea has been historically concentrated among MSM in Australia,<sup>12</sup> there has been a 475% increase in gonorrhoea notifications among females in the state of Victoria, Australia, from 2010 to 2019.<sup>13,14</sup> Similarly, whereas syphilis diagnoses in Australia remains concentrated among MSM residing in inner urban locations, syphilis is increasing in heterosexual men and women in Australia, especially those residing outside of inner-city suburbs.<sup>15</sup> Although the reasons for STI increases among heterosexuals in outer-suburbs are not fully understood, they may be reflective of less access of sexual health services.<sup>14</sup> Australian HIV surveillance data shows that, for HIV, women are often diagnosed late and report no prior history of HIV testing.<sup>16</sup> Genomic analyses also suggest that transmission of gonorrhoea into heterosexual populations may be facilitated through the bridging of sexual networks via populations of men who have sex with men and women.<sup>17</sup>

Further, although the burden of STIs among young heterosexuals has been well described, more evidence is coming to light of emergent STI epidemics among older heterosexual populations. In the US, the Centers for Disease Control and Prevention (CDC) reports a doubling of STIs among those aged >65 over the last 10 years.<sup>18</sup> Reasons for increasing STI rates among older populations may relate to lower levels of sexual health knowledge<sup>19</sup> and inaccurate risk perception<sup>20</sup> among older generations.

### Men who have sex with men

Although STI epidemics may be diversifying beyond traditional risk groups, STI burden remains clustered within networks of people who may share specific risk practices

with high rates of assortative partner mixing. MSM are at increased risk of STIs due to a combination of biological and behavioural factors (e.g. more partners, more concurrent partners, type of partners) and the relative prevalence of STIs within sexual networks that contributes transmission risk. Although MSM are recognised as a priority group for STIs globally, the population of MSM comprises a diverse group, with different behaviours, identities and healthcare needs, and consequently risk varies across specific subgroups. For example, MSM living with HIV have historically had higher rates of STIs such as syphilis<sup>21</sup> and sexually acquired hepatitis C,<sup>22</sup> likely associated with smaller sexual networks with high rates of partner mixing, which sustain high prevalence and onward transmission. Given the often differing prevalence of STIs between HIV-negative MSM and MSM living with HIV, and specific sexual network dynamics, behavioural and demographic predictors of STI risk often vary between the two groups.<sup>23</sup> Further, rates of specific STIs within risk populations often vary based on age. For example, among MSM in Australia, gonorrhoea is more common among those aged 20–29 years compared to syphilis, which is most common among those aged 30–39 years.<sup>24</sup>

The concentration of STI risk among subgroups of MSM is also diversifying. Advances in biomedical interventions for HIV over the past decade, including Treatment as Prevention (TasP) and pre-exposure prophylaxis (PrEP), have led to changes in behaviour and STI epidemiology among MSM. Although declines in condom use at the population<sup>25,26</sup> and individual level<sup>27–29</sup> associated with the roll-out of PrEP in high-income countries have occurred in parallel to increases in STI incidence,<sup>30,31</sup> disentangling and quantifying the direct effect of PrEP rollout on STI incidence is difficult.<sup>32</sup> Some countries that have seen significant uptake of PrEP were observing increases in STIs and declines in condom use among MSM prior to this scale-up.<sup>33</sup> Even prior to epidemiological evidence emerging, assumptions regarding declines in condom use in the context of PrEP has led to specific STI testing guidelines for PrEP delivery.<sup>34</sup> STI testing guidelines for PrEP also acknowledge the risk-based criteria for PrEP prescribing<sup>35–37</sup> and high rates of STI diagnosis prior to PrEP initiation.<sup>30,38</sup> Surveillance data from Australia, where PrEP has been available since early 2016 through large demonstration projects<sup>39,40</sup> and more widely available since April 2018 when PrEP was approved as a government subsidised medicine, have shown that, although rates of chlamydia and gonorrhoea have stabilised among MSM using PrEP, syphilis continues to increase.<sup>41</sup> Continuing increases in syphilis among PrEP users is likely reflective of greater comfort in,<sup>42</sup> and increased rates of,<sup>43</sup> serodiscordant sex in the era of HIV TasP and PrEP, and the greater differential in syphilis prevalence between MSM living with HIV and HIV-negative MSM compared to chlamydia and gonorrhoea. Further still, within risk groups such as PrEP users, the burden of STIs is highly skewed

towards those experiencing repeat or concurrent infections. Analysis of PrEP users enrolled in an early demonstration project in Australia found that 50% of PrEP users were not diagnosed with an STI during follow up, and that one-quarter of PrEP users accounted for three-quarters of STIs.<sup>30</sup> These trends have continued to be observed into the years following widespread PrEP implementation in Australia<sup>41</sup> and in other settings such as the UK.<sup>44</sup>

## Travellers and migration

With early detection and treatment of STIs to prevent onwards transmission a key STI prevention strategy, there is an increasing focus on the impact of higher risk behaviours and settings associated with international travel and migration on local STI transmission. International travellers returning from high-prevalence settings are at increased risk of STIs,<sup>45</sup> and if not identified upon arrival, risk introducing new strains of STIs and seeding new clusters of transmission. Pre-emptive sexual risk screening during clinical visits prior to travel, for example for vaccines, could provide an opportunity to offer STI interventions, such as STI immunisation, PrEP or self-initiated antibiotic treatment of bacterial STIs, while also prompting travellers to be screened for STIs when they return.<sup>46</sup>

Migrants arriving in high-income countries often face additional barriers to accessing sexual health care driven by cultural aspects of stigma, knowledge gaps in health literacy, and ineligibility for subsidised care.<sup>47</sup> For example, in Australia, newly arrived Asian-born MSM have been identified as an emerging priority group for HIV,<sup>48</sup> with qualitative work highlighting that lack of access to subsidised PrEP introduces a cost barrier for many newly-arrived MSM.<sup>49</sup> Similar structural barriers exist for access to routine HIV and other STI testing for this group, which potentially contribute to higher observed incidence of HIV among Asian-born MSM and high rates of testing positive for HIV at first presentation for testing.<sup>50</sup> The impact of inequitable access to health care on STI risk may be compounded by changes in sexual risk-taking behaviour following migration, especially among MSM emigrating from countries with typically repressive social norms to countries with more progressive views and greater access to gay venues and community.<sup>51</sup> Similarly, migrant sex workers are often at greater risk of STIs than non-migrant sex workers, although the interaction between migrant status and country income level has been shown to vary depending on local epidemiology and legal contexts.<sup>52</sup> STI risk has been shown to be higher among migrant sex workers who do not have contact with outreach workers,<sup>53</sup> further highlighting the impact of unequal access to health care and harm-reduction services on STI risk among migrant populations. Lastly, movement across communities within countries may also be contributing to STI transmission. Recent modelling work suggests that high population

mobility likely contributes to high levels of STI prevalence among remote indigenous communities in Australia.<sup>54</sup>

## Technology and risk environments

Across a diverse range of traditional and non-traditional risk groups, specific behaviours may be associated with particular risk environments or the use of digital technologies to meet partners that pose challenges for risk-based screening in clinics and for targeted interventions and health promotion. For example, among MSM, meeting partners at sex-on-premises venues may be associated with increased risk, as STI prevalence is high among MSM attending these venues.<sup>55</sup> Meeting partners online or through 'hookup' apps has also been shown to be associated with greater STI risk among MSM.<sup>56</sup> For heterosexual people, although a recent review found no evidence of an association between online-partner seeking and lower condom use or STI status,<sup>57</sup> among young heterosexual people, use of geo-social dating apps has been linked to increased rates of casual sex, having multiple partners and having sex without discussion about STI status.<sup>58</sup> Other subcultural behaviours associated with increased STI risk, such as 'swinging'<sup>59</sup> may not be readily identified at STI clinics. Practices such as those mentioned above typically cluster within specific geographic and social or sexual networks, and therefore relative risk can be temporally and significantly elevated in the context of undiagnosed infections entering specific networks, resulting in outbreaks of STI infections.

With more evidence of diversifying STI risk, there is a need to go beyond broad, risk-group categorisations based on age, sex and sexuality. Risk diversification poses significant challenges, not only in terms of risk-based diagnostic testing, but also in relation to the costs and resources associated with reaching a broader range of constituents with preventive and health promotion interventions. Here, continued STI surveillance and research, including qualitative and ethnographic research to understand contextual factors that drive risk, is important and emerging data need to be monitored closely to guide and inform policy and practice. Early detection of risk diversification is crucial, given STI control becomes increasingly challenging as prevalence increases in emergent risk populations. Strategies must continue to promote high intervention coverage among known risk groups, but also consider targeted interventions that focus on individuals at greatest risk within these groups.

## Rethinking risk – more than just behaviours

As described above, defining traditional risk groups on the basis of broad demographic and sexual behaviour may be inadequate for efficient and effective STI prevention and clinical interventions. To guide targeted interventions towards those at greatest risk, strategies that include

non-behavioural considerations may be beneficial. For example, although condom use may be strongly associated with HIV risk, there is mixed evidence of the association between condom use and STI risk, relative to other factors; evidence suggests that among MSM using PrEP, condom use is less predictive of STI risk than sexual networks and the practices that contribute to defining these networks.<sup>30</sup> The estimated per-partner effectiveness of condoms for bacterial STIs<sup>60</sup> is also much lower than for HIV,<sup>61,62</sup> and high levels of extra-genital transmission of STIs among MSM have been reported.<sup>63</sup> Practitioners should therefore consider, dependent upon local epidemiology and context, a broader suite of factors when screening for risk, beyond traditional notions of broad demographic risk or condom-based definitions of 'safe sex'.

## Neighbourhoods and access to health care

Key drivers of STI risk are not purely behavioural, but relate to STI prevalence within respective communities and sexual networks, as well as individuals' access to sexual health care and testing. Less access to testing and health care means that STIs remain undiagnosed for a long period of time, and individuals have more chance of passing infections on to their sexual partners. This is evident among populations of black MSM in high-income countries such as the US, the UK and Canada, who are at increased risk of HIV compared to white MSM, despite there being no evidence that black MSM have more partners or engage in more serodiscordant condomless sex than other MSM.<sup>64</sup> A wealth of data highlights that black MSM in the US are often faced with poor access to culturally competent health services, including HIV and STI testing, and experience stigma and discrimination that impede access to services.<sup>65</sup> Similarly, Aboriginal communities living in remote regions of Australia experience disproportionately high rates of STIs, with chlamydia and gonorrhoea prevalence among young people in these communities among the highest in the world.<sup>66,67</sup> With others demonstrating similar numbers of sexual partners and a similar average age at sexual debut among young Aboriginal Australians compared to non-Indigenous young people,<sup>68</sup> discrepancies in STI incidence are likely driven by structural barriers (e.g. access to testing affecting rates of undiagnosed infections). Despite clinical guidelines and specialist support for primary healthcare clinicians visiting these remote communities, rates of re-testing and clinical follow up within recommended timeframes in Aboriginal communities are suboptimal.<sup>69</sup> Remote Aboriginal communities are faced with significant clinician-level barriers to STI testing, such as high levels of clinician turnover, a lack of familiarity with STI protocols, and prioritisation of other urgent health concerns by clinicians.<sup>70</sup> The impact of access to health care on HIV outcomes is also reflected in Australian migrant communities, especially those from South-East Asia and Sub-Saharan Africa and those from countries that

are ineligible for reciprocal healthcare agreements, where larger gaps in the HIV care cascade are observed compared with non-migrants.<sup>71</sup> Lower rates of repeat HIV testing are also observed among HIV-negative migrants.<sup>50</sup> Addressing disproportionate rates of STIs among both Aboriginal and migrant communities will require systemic change and removal of structural barriers to accessing health care.

Further highlighting the important role of environmental and socio-structural factors in contributing to STI risk, differences in laws and practices that maintain racialised inequities (e.g. inequitable urban housing policies) at the neighbourhood level have been shown to be greater predictors of HIV risk than sexual risk behaviours.<sup>72</sup> In the US, higher rates of gonorrhoea have been linked to neighbourhood-level determinants of health, including higher rates of single mothers and lower socio-economic status.<sup>73</sup> Analysis of syphilis distribution in Canada suggests that spatial clustering of syphilis diagnoses is not fully explained by distribution of MSM populations or different rates of testing across areas, suggesting that additional neighbourhood-level factors are likely driving transmission.<sup>74</sup> These data highlight the importance of localised surveillance and research to ensure risk is appropriately understood and addressed within local contexts.

## Changes in risk

It is also important to consider that risk changes over time, and that if an individual does not meet certain risk criteria for screening or a prevention intervention, they may in the future. For example, early PrEP guidelines in Australia recommended prescribing PrEP even in the absence of recent risk, if individuals anticipated risky behaviour in the near future.<sup>34</sup> Similar considerations for STI interventions should be considered. Latent transition analysis among both heterosexuals<sup>75</sup> and gay and bisexual men<sup>76</sup> show that individuals' allocation into specific risk groups remains relatively stable. However, changes in risk are often observed when people move out of monogamous relationships. This is reflected in risk-based STI guidelines for young heterosexuals,<sup>77</sup> and latent transition analysis of MSM regularly attending for STI testing.<sup>76</sup> Further, these data reflect states of risk prior to the introduction of PrEP. Given the evidence of changes in STI risk follow PrEP initiation,<sup>27</sup> and that people transition in and out of PrEP use based on personal risk perception over time,<sup>78</sup> regular assessment of current risk among people presenting to health services with any history of PrEP use is warranted. Further, the coronavirus disease 2019 (COVID-19) pandemic and associated public health orders have led to significant changes in sexual behaviour<sup>79</sup> and breaks in PrEP use<sup>80,81</sup> among MSM, decreases in casual sex among heterosexuals,<sup>82</sup> and significant declines in the frequency of STI testing.<sup>83</sup> Drops in testing in the presence of

ongoing sexual risk have the potential to increase pools of undiagnosed infection.

## Screening for STIs

Although testing is crucial for the control of STIs, guidelines on who to test, and how often, vary. Many guidelines highlight specific populations that should be considered for STI screening, or recommend clinicians take a sexual history to determine if individuals should be screened. Among populations where STIs are highly asymptomatic (e.g. extra-genital infections among MSM), informed decisions around how to screen in the absence of symptoms rely on understanding epidemiological contexts (historical and emerging). Although broad-based guidelines, which recommend testing of entire populations (e.g. regular testing of all sexually active MSM or STI testing at each PrEP prescribing visit), may lead to greater testing coverage and frequency, they present challenges for managing clinic capacity and may impact the cost and cost-effectiveness of sexual health services. Such strategies consume a lot of resources and are not often feasible in resource-constrained settings or where testing is not fully subsidised. Further, broad-based recommendations obfuscate the need for nuanced risk screening and targeted higher frequency testing for those at particularly high risk or those who are diagnosed with STIs recurrently.

## Opportunistic testing during routine visits

Opportunistic testing, when a test is offered in-clinic during a routine patient visit, often occurs after clinicians take a sexual history, following an electronic prompt, or if the patient is identified as belonging to a specific high-risk group for which STI testing is recommended. For example, in the US, the CDC and US Preventive Services Task Force recommend annual chlamydia and gonorrhoea screening for all sexually active females aged <25 years, and annual screening for women aged >25 years with a risk factor (more than one sex partner, a sex partner with concurrent partners, a new partner).<sup>84</sup> Although such recommendations allow clinicians to assess risk on an individual basis, significant challenges associated with risk screening exist. Clinician barriers include discomfort around engaging in sexual health discussion or asking sensitive questions, feeling inadequately trained, and difficulty incorporating a sexual screen into a regular visit due to time constraints.<sup>85</sup> Barriers may also be magnified among doctors who serve ethnically diverse populations.<sup>86</sup> Patient sexual history may also be hindered due to patient concerns around confidentiality and stigma, lack of perceived risk and lack of sexual health awareness.<sup>87</sup> Some of these barriers can be overcome by implementing computer-assisted self-interviewing in clinic waiting rooms, where patients

complete an electronic survey that asks about their sexual history and specific risk factors.<sup>88</sup>

## Universal screening of key populations

In contrast to its screening recommendations for women (women aged <25 years screened annually, those aged >25 years only screened if a risk factor is present), the US CDC recommends annual screening for all sexually active MSM, and more frequent screening (3–6 months) for MSM at increased risk (defined as having multiple partners or persistent risk behaviours).<sup>89</sup> In Australia, guidelines were updated in 2019 by removing specific risk-based recommendations for screening frequency among MSM and recommending uniform 3-monthly testing for bacterial STIs for all sexually active MSM, regardless of the number of partners, STI history or presence of specific risk behaviours.<sup>90</sup> Although increasing rates of STIs among MSM may warrant high-frequency screening, in the context of highly skewed STI incidence among certain subgroups of MSM<sup>41</sup> and resource and time constraints in general practice, not distinguishing between high- and low-risk MSM may lead to ineffective or less cost-effective STI screening practices.

It is not clear whether the implementation of ambitious guidelines, which recommend high-frequency screening for all MSM regardless of risk-factors, such as those in Australia, will lead to greater increases in testing frequency among those already being tested, or in testing coverage across the whole population, with little evidence to suggest this strategy would have an impact on STI prevalence. Although sexual health clinics may be able to achieve such testing rates, in jurisdictions where STI testing is mainly conducted in general practice, the burden of trying to screen all MSM four times a year might mean adequate screening is not achieved among those who it would benefit the most, and universal screening at high frequency is likely not feasible in settings where testing is not covered by universal healthcare arrangements.

## Effect of screening on STI prevalence

Evidence for the effectiveness of broad-based population-level screening on test uptake and STI prevalence is mixed, and the benefits and harms of broad-based population testing versus more specific risk-guided testing protocols vary between population. Risk-based opportunistic screening in the US, based on taking a sexual history, has largely not been successful in achieving high rates of chlamydia screening among high-risk young women,<sup>91</sup> largely due to low rates of practitioners in general practice undertaking a sexual history. A 2006 survey found that only 55% of primary care physicians asked about sexual histories as part of regular examinations.<sup>92</sup> Data from Australia reports that

46% of general practice clinicians would not take a sexual history of MSM presenting for a routine check up.<sup>85</sup>

Even if clinician- and patient-level barriers are overcome, there is little evidence to suggest that high coverage of opportunistic screening among heterosexuals has an impact on STI prevalence. A large cluster randomised controlled trial of opportunistic chlamydia testing in rural GP services in Australia, which implemented a protocol involving clinician education, computer alert prompting and reimbursements, found that even with increased testing of eligible patients, the intervention was not associated with a decline in chlamydia prevalence.<sup>93</sup> However, it was associated with a decline in PID presentations at nearby hospitals. Additional data from the US shows that although screening among heterosexuals may not reduce chlamydia prevalence, it is a potentially effective approach to reduce PID.<sup>94</sup> Another large cluster-randomised controlled trial, which assessed a multi-pronged intervention of continuous quality improvement (review of clinical data, education, implementation of systems-level changes aimed at improving STI practice) in general practice clinics serving remote indigenous populations in Australia, again found increases in testing, but no changes in population-level prevalence of STIs.<sup>95</sup>

## Strategies to increase STI testing capacity

Consideration of adapted service models and strategies to enhance STI testing efficiency in established services may be required to maintain capacity for broad risk-based STI screening practices, while also increasing testing coverage and frequency among those at particularly high risk. Although technology-based systems to reduce the burden of high frequency testing on patients have been implemented at the clinic and laboratory level (e.g. results delivered by SMS<sup>96</sup>), frequent testing can be challenging because of restricted clinic operating times. These types of health systems barriers make increasing patient-driven demand for STI testing difficult. For example, evaluation of a large Australian health promotion campaign targeting MSM for HIV and STI testing found that despite substantial investment in health promotion and a high proportion of MSM recalling campaign messages, only a modest increase in chlamydia and gonorrhoea testing was achieved, and the campaign had minimal impact on HIV or syphilis testing.<sup>97</sup> Social marketing initiatives aimed at creating demand for testing must also be accompanied by structural changes that make STI testing more convenient.

In order to achieve high rates of testing, adaptive and convenient service models that reduce the burden on patients will be required. A recent scoping review of HIV and STI testing preferences among MSM in high-income countries identified the convenience and privacy of self-testing, and the need to provide a variety of testing options, as key themes of testing preferences.<sup>98</sup> A 2016 review of interventions aimed at increasing STI screening found that

the most effective interventions included incorporating collection of STI specimens as standard procedure regardless of the reason for the visit, and the use of electronic health records as a reminder to offer screening.<sup>99</sup> Models that streamline clinic visits, including patients self-collecting specimens, computer-assisted questionnaires, test-and-go services, and rapid testing with same-day results, have been shown to increase screening while also reducing costs and time between testing and treatment.<sup>100</sup> The incorporation of all these elements into a single, free, express testing service, Dean Street Express in London, was shown to reduce mean time between test and notification to 0.27 days, compared to the standard clinic's 8.95 days, which was projected to have prevented 196 chlamydia and/or gonorrhoea infections over 1 year after implementation.<sup>101</sup> Nurse-led test-and-go services, which remove the need for doctor consultation and reduce testing times, have also been shown to capture clients with different demographics, yet still detect a similar rate of STI positivity, compared to standard doctor-led testing.<sup>102</sup>

### **Opt-out testing**

Another strategy, opt-out testing, involves testing all patients in a specific risk group, regardless of the presence of sexual risk factors, with the aim of increasing screening rates. Population-based opt-out screening methods remove the burden of clinicians to initiate sexual history taking, and decide if a test is appropriate or needed. However, opt-out testing does place the burden on clinicians to ensure appropriate disclosure of the test to patients in pre-test discussions to ensure they are aware of the implications of a positive result and have the opportunity to opt out. Surveillance data from Australia showed opt-out testing increased rates of syphilis testing among MSM living with HIV.<sup>103</sup> Modelling work suggests that an opt-out testing strategy for all women aged 15–24 years in the US would likely reduce chlamydia prevalence, and be more cost-effective compared to a risk-based screening strategy; however, this was dependent on individuals' insurance coverage.<sup>104</sup> In limited-resource settings or where universal health care is not available, overall effectiveness and cost-effectiveness of such strategies would be significantly reduced.

### **Targeted testing of those at greatest risk**

A modelling study of syphilis among Canadian MSM found that increasing screening frequency among those already engaged in testing had a greater reduction on syphilis incidence than increasing screening coverage (i.e. the proportion of the population tested).<sup>105</sup> Another modelling study of MSM in the US found that both increasing the rate of screening from current levels to biannual among all sexually active MSM currently being tested, and increasing

the coverage of biannual screening to 30% of all 'high-risk' MSM, each reduced chlamydia and gonorrhoea incidence by approximately a 75% reduction over 10 years. The authors suggest that more frequent screening for all MSM, and scaling up targeted screening for men with multiple recent partners, were the most effective strategies.<sup>106</sup> US guidelines recommend syphilis screening in MSM, people with HIV and pregnant women, but do not provide routine screening recommendations for HIV-negative heterosexual populations. Modelling work suggests that achieving such a strategy may have an impact on transmission in states with more MSM-focused outbreaks, but would have little or no impact on transmission in states where syphilis is more evenly distributed between MSM and heterosexual populations.<sup>107</sup>

Guiding public health strategies to increase active case-finding using epidemiological trends can quickly and efficiently respond to new STI outbreaks. For example, many countries utilise existing networks of general practice clinicians to issue alerts around increasing rates of STIs in certain geographical areas or subpopulations. In the UK, outbreaks are detected by local surveillance undertaken by clinicians or health protection teams via the detection of higher than expected numbers of diagnoses.<sup>108</sup> These are sometimes supplemented by more systematic approaches that utilise automated spatiotemporal detection tools to routinely analyse notification data.<sup>109</sup> Following an investigation to declare and determine the spread of an outbreak, initial stages of outbreak response usually involve alerting clinicians and appropriate organisations through established communication systems. Similar alerts in Australia are commonly issued through the general practitioner network.<sup>110</sup> Sustained outbreak control can then include strategies such as active case-finding, qualitative data collection to understand drivers of the outbreak, outreach programs targeting specific venues or populations, and widespread promotion through social and traditional media.<sup>108</sup> These strategies can also facilitate targeted communication to non-primary care clinicians who may not be routinely involved in STI care. For example, recent increases in congenital syphilis, likely related to low rates of syphilis screening and issues with continuity of care and treatment during pregnancy among patients tested in antenatal hospital clinics in Australia,<sup>111</sup> led to specific guidance targeted at increasing syphilis testing during pregnancy. The success of such strategies relies on surveillance infrastructure to identify and characterise new STI outbreaks in a reliable and timely manner, and appropriate levels of funding and technical support to resource a timely response.

### **Over-screening**

In addition to the burden of frequent STI testing incurred by the patient, there are potential harms associated with over-screening for STIs, including anxiety, psychological harm

associated with false positives or negatives, or possible change in risk behaviour. However, the US CDC reports there is currently limited data on psychological or other harms associated with screening for chlamydia and gonorrhoea among women and heterosexual men.<sup>112</sup> Among MSM, there is growing evidence that high antibiotic consumption among PrEP users may be driving antibiotic resistance. Given high rates of bacterial STIs among PrEP users, and high frequency screening and treatment, PrEP users have high levels of macrolide consumption, as well as for cephalosporins, fluoroquinolones and tetracyclines.<sup>113</sup> In some European countries, consumption of macrolides is 52-fold higher among PrEP users compared to community-level consumption.<sup>113</sup> Cohorts of PrEP users around the world are commonly characterised by having high rates of partner change,<sup>27</sup> translating to high and stable prevalence of chlamydia and gonorrhoea. Long-term surveillance data in Australia suggest that sustained high-frequency testing of PrEP users (3-monthly) for >4 years has not curbed rates of chlamydia or gonorrhoea in this group.<sup>41</sup> In contrast, such high-frequency screening is costly and may be driving antimicrobial resistance.<sup>114</sup> Modelling work suggests that even low levels of screening for the largely asymptomatic STI *Mycoplasma genitalium* among MSM is leading to increased antibiotic resistance through increased, arguably unnecessary treatment.<sup>115</sup> In its resistance threats 2019 report, the US CDC has listed drug-resistant gonorrhoea on its Urgent Threats list, and *Mycoplasma genitalium* on its watch list.<sup>116</sup> Surveillance of antimicrobial resistance is crucial in the context of high-frequency screening and transmission. In light of the threat of antimicrobial resistance, there is a growing case for reconsidering the evidence base for high-frequency screening of STIs, which are mostly asymptomatic, among populations with high and stable prevalences.<sup>117</sup>

## Identifying risk

With the aforementioned barriers to clinician-led discussions on sexual history during routine care, and the need for increased client-driven demand for testing, methods to appropriately and efficiently identify risk, both from the clinician perspective and including individuals' self-perception of risk, are crucial.

### Service-identified risk

For clinical services aiming to identify risk, strategies can go beyond broad testing protocols based on risk group and the use of clinical data and automated screening tools. For example, previous infection can be used as an indicator of risk. History of an STI has consistently been shown to be one of the strongest indicators of future risk among both MSM<sup>118</sup> and adolescent heterosexuals.<sup>119</sup> The strong predictive value of a

previous diagnosis is reflective of high rates of reinfection, such as that of syphilis reinfection widely observed among MSM,<sup>120</sup> especially those living with HIV.<sup>118</sup> It is unsurprising then that modelling work suggests that increasing screening frequency among MSM with a prior syphilis diagnosis is equally effective in reducing syphilis prevalence as testing focused on those reporting high partner numbers, and far more effective than distributing testing equally among all MSM.<sup>121</sup> Targeting individuals with a prior diagnosis of syphilis can be done through clinician-led history taking, patient management system alerts or through demand-creation approaches such as community-driven awareness-raising of reinfection risk.

Novel methods for identifying those at risk, including machine learning and prediction modelling using electronic medical records, have also been explored, with varying levels of efficacy. For example, the use of computer-assisted sexual history taking allows data on behavioural risk factors to be analysed using risk prediction models and machine learning. Machine learning has been successfully used to identify those who are eligible for PrEP based on medical records;<sup>122</sup> however, the use of machine algorithms of structured health record data have been shown to poorly differentiate patients with and without repeat STI diagnosis, indicating that they may be less useful for predicting STI risk.<sup>123</sup> Prediction models of routinely collected healthcare data have been used in emergency room settings where laboratory variables are collected and can be used for risk prediction.<sup>124</sup> Despite growing work on machine learning, such techniques require technical capacity, education and training, and access to 'big data' through which to generate predictive algorithms. Also, as prediction methods rely on patient history, they would likely provide less benefit in determining STI risk for patients attending clinics sporadically or for the first time.

### Risk self-identification

Along with clinical services being able to adequately identify STI risk, patient-driven demand for STI testing relies heavily on individuals recognising their own risk, and seeking STI testing. An analysis of adults in the UK found that both men and women underestimate their self-risk of STIs, and that many who did perceive themselves as at-risk had not recently accessed STI care.<sup>125</sup> Health promotion, therefore, should not only focus on improving self-identification of risk, but also encourage people to act on their perceived self-risk by accessing care. Perception of the seriousness of STIs has been shown to vary considerably among specific subgroups of MSM at high risk of STIs,<sup>126</sup> and may influence an individual's decision to present for testing following possible exposure to an STI or following windows of risk, if they perceive the health risk of an STI going undiagnosed to be low. Along with perceptions of risk, STI knowledge has also been linked to recent STI testing,<sup>127</sup>

highlighting the importance of health promotion campaigns for increasing STI awareness and access to information on STIs. Peer-led models of care have been shown to provide opportunities for MSM to enhance their risk-reduction knowledge around STIs, with greater benefits among young and less gay community-attached MSM.<sup>128</sup>

Finally, technology is also playing a role in the self-identification of STI risk. As described earlier, MSM who use geo-social networking apps are at increased risk of STIs. This highlights a potential opportunity for community and health organisations to deliver reliable, trusted and easily accessible sexual health information at scale to those at greatest risk via social networking apps. Further, specific mobile phone applications have been designed to screen for STI risk, as well as to help users identify STI symptoms. Although mobile phone apps for the care and prevention of STIs are of high interest to the general public,<sup>129</sup> a 2016 review of available STI-related apps found that many contained incorrect and potentially harmful information.<sup>130</sup> Recent data also suggest that although digital methods of sexual healthcare delivery (i.e. through video consultation) may be acceptable, many still prefer human interaction over automated chat-bots when accessing sexual health information.<sup>131</sup> Further, disparities in utility and uptake of digital health information and interventions exist, with older people<sup>132</sup> and those from racial and ethnic minorities less likely to engage in technology-based interventions.<sup>133</sup>

## Conclusion: adopting an adaptive risk-guided approach to STI control

Alongside historically high-risk groups, new risk groups for STIs continue to emerge and diversify. Although the evidence for the effect of population-based screening compared to higher frequency, targeted screening strategies on STI prevalence varies within and across MSM and heterosexual populations and for specific STIs, strategies that reduce clinician- and patient-level barriers, and are adaptive to local epidemiological contexts, have the greatest potential for achieving optimal screening rates and controlling new outbreaks. Such strategies need to remove the burden on clinicians and the assumption of risk, and improve patient convenience in order to increase testing coverage, while still including sufficient nuances to identify those at greatest risk for targeted testing and prevention.

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**Data availability.** Data sharing is not applicable as no new data were generated or analysed during this study.

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## RESEARCH ARTICLE

## REVISED The impact of condom use on the HIV epidemic [version

## 2; peer review: 2 approved]

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**Abstract**

**Background:** Condom promotion and supply was one of the earliest interventions to be mobilized to address the HIV pandemic. Condoms are inexpensive and provide protection against transmission of HIV and other sexually transmitted diseases (STIs) as well as against unintended pregnancy. As many as 16 billion condoms may be used annually in all low- and middle-income countries (LMIC). In recent years the focus of HIV programs has been on testing and treatment and new technologies such as PrEP. Rates of condom use have stopped increasing short of UNAIDS targets and funding from donors is declining.

**Methods:** We applied a mathematical HIV transmission model to 77 high HIV burden countries to estimate the number of HIV infections that would have occurred from 1990 to 2019 if condom use had remained at 1990 levels.

**Results:** The results suggest that current levels of HIV would be five times higher without condom use and that the scale-up in condoms use averted about 117 million HIV infections.

**Conclusions:** HIV programs should ensure that affordable condoms are consistently available and that the benefits of condom use are widely understood.

**Keywords**

Condoms, HIV prevention, modeling

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**REVISED Amendments from Version 1**

This version has updates that respond to reviewers comments. It adds detail on data sources, more detail on the equations and expands the discussion.

**Any further responses from the reviewers can be found at the end of the article**

## Introduction

The distribution and promotion of condoms has been a part of efforts to prevent HIV transmission since the beginning of the HIV response. Early programs often focused on ABC (Abstinence, Be faithful, use Condoms). Condoms provide triple protection, against the transmission of HIV and other sexually transmitted infections as well protection against unintended pregnancy<sup>1</sup>. Condom social marketing programs were the first HIV programs to reach national scale in many countries. The number of condoms distributed through social marketing programs increased from about 590 million annually in 1991 to 2.5 billion by 2012 before declining to about 1.7 billion in 2019<sup>2</sup>. Across 55 countries with a recent national household survey as part of the Demographic and Health Surveys (DHS) or AIDS Indicator Surveys (AIS) about 60 percent of men reported using a condom the last time they had sex with a non-marital, non-cohabiting partner and 65 percent report using a condom the last time they visited a sex worker (Table 1).

In all low- and middle-income countries about 16 billion condoms are used annually with about 7.5 billion used primarily for HIV prevention<sup>1</sup>. Since these figures are based on self-reports of condom use, they may over-state actual use. However, it is clear that large numbers of condoms have been procured and/or distributed with the intention of helping users prevent HIV transmission.

Studies have shown condoms to be highly effective against HIV<sup>3</sup>, other sexually transmitted infections<sup>4</sup> and unintended pregnancy<sup>5</sup>. Consistent use is required to maximize an individual's protection. However, even inconsistent use will provide some benefit that can be large at a population-level<sup>6</sup>.

Across all DHS surveys about three-fifths of people report relying on the public sector for their condom supply. Social marketing programs provide nearly 2 billion condoms each year (<https://www.dktinternational.org/contraceptive-social-marketing-statistics/>), about Thus, international donor and national government funding for condom purchase, distribution and promotion plays a large role in supporting the widespread use of condoms.

The purpose of this paper is to investigate the global impact of condoms on the HIV epidemic through both retrospective and prospective analyses.

## Methods

We used a publicly available mathematical simulation model, the [Goals model](#)<sup>7</sup>, to examine the impact of past and future

condom use on the AIDS epidemic in 77 high burden countries. We used version 6.06 of the Goals model, which is available for free download at <https://www.avenirhealth.org/software-spectrum.php>. The source code for the calculations is available as *Extended data*<sup>8</sup>. This is the same model that was used to estimate epidemiological impact for the new UNAIDS Global HIV Strategy<sup>9</sup>.

Goals is a simulation model that calculates HIV transmission among different population risk groups (monogamous heterosexual couples, those with multiple heterosexual partners, female sex workers and clients, men who have sex with men (MSM), and people who inject drugs (PWID)) on the basis of their behaviors (number of partners, contacts per partner, condom use, age at first sex, needle sharing) and characteristics that influence transmission (presence of other sexually transmitted infections, stage of infection, male circumcision, and use of antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP)). The model uses data on behaviors drawn from national surveys, such as DHS, and program data on the coverage of ART and programs to prevent mother-to-child transmission, PMTCT, from UNAIDS' HIV database. The model is fit to official estimates of HIV prevalence trends for each country, also available from UNAIDS.

HIV transmission is calculated as a function of epidemiological factors and the behavioral factors listed above. For uninfected people in each risk group, the probability of becoming infected in a year is given by the following equation:

$$P_{s,r,t} = \{1 - [Prev_{s',r,t} \times (1-r_s \times S_{s,r,t} \times STI_{s,r,t} \times MC_{r,t} \times C_{r,t} \times PrEP_{s,r,t} \times ART_{s,r,t})^a + (1-Prev_{s',r,t})]^n\}$$

Where:

$P_{s,r,t}$  = Annual probability of becoming infected for a person of sex  $s$  in risk group  $r$  at time  $t$

$Prev_{s',r,t}$  = HIV prevalence in the partner population in risk group  $r$  at time  $t$

$r_s$  = probability of transmission per sex act by type of act (heterosexual, homosexual)

$S_{s,r,t}$  = multiplier based on the stage of infection (primary stage, chronic stage or late stage)

$MC_{r,t}$  = multiplier based on male circumcision status

$STI_{r,t}$  = multiplier based on STI prevalence

$C_{r,t}$  = multiplier based on condom use

$PrEP_{r,s,t}$  = multiplier based on the use of PrEP

$ART_{s,t}$  = multiplier based on ART use

$a_{r,t}$  = number of acts per partner per year in risk group  $r$  at time  $t$

$n_{r,t}$  = number of partners per year in risk group  $r$  at time  $t$

**Table 1. Reported rates of condom use at last sex with a higher risk partner and with a sex worker.**

Country	Year and survey	Percentage reporting condom use at last higher risk sex	Percentage reporting condom use at last paid sex	Country	Year and survey	Percentage reporting condom use at last higher risk sex	Percentage reporting condom use at last paid sex
Albania	2017–18 DHS	58	65	Kenya	2014 DHS	76	74
Angola	2015–16 DHS	53	71	Kyrgyz Republic	2012 DHS	83	95
Armenia	2015–16 DHS	82	84	Lesotho	2014 DHS	77	90
Azerbaijan	2006 DHS	35	53	Liberia	2013 DHS	42	61
Benin	2017–18 DHS	36	44	Madagascar	2008–09 DHS	13	13
Bolivia	2008 DHS	50	89	Malawi	2015–16 DHS	73	75
Burkina Faso	2010 DHS	74	33	Mali	2018 DHS	39	70
Burundi	2016–17 DHS	51	55	Moldova	2005 DHS	54	
Cambodia	2014 DHS	74	82	Mozambique	2015 AIS	47	31
Cameroon	2018 DHS	63	83	Myanmar	2015–16 DHS	77	77
Chad	2014–15 DHS	42	50	Namibia	2013 DHS	80	67
Colombia	2015 DHS	71	85	Nepal	2016 DHS	68	93
Comoros	2012 DHS	60	65	Niger	2012 DHS	64	
Congo	2011–12 DHS	58	75	Nigeria	2018 DHS	65	74
Congo Democratic Republic	2013–14 DHS	31	34	Papua New Guinea	2016–18 DHS	33	48
Cote d'Ivoire	2011–12 DHS	63	63	Philippines	2003 DHS	24	36
Dominican Republic	2013 DHS	71	80	Rwanda	2014–15 DHS	66	65
Eswatini	2006–07 DHS	67		Sao Tome and Principe	2008–09 DHS	61	76
Ethiopia	2016 DHS	51	81	Senegal	2019 DHS	72	
Gabon	2012 DHS	75	83	Sierra Leone	2019 DHS	23	57
Gambia	2013 DHS	67	69	South Africa	2016 DHS	73	83
Ghana	2014 DHS	39	44	Tanzania	2011–12 AIS	60	
Guatemala	2014–15 DHS	68	80	Timor-Leste	2016 DHS	34	40
Guinea	2018 DHS	50	72	Togo	2013–14 DHS	61	62
Guyana	2009 DHS	72	82	Uganda	2016 DHS	62	73
Haiti	2016–17 DHS	63	90	Ukraine	2007 DHS	62	84
Honduras	2011–12 DHS	61	32	Vietnam	2005 AIS	73	
India	2015–16 DHS	41	48	Zambia	2018 DHS	54	56
Indonesia	2012 DHS		34	Zimbabwe	2015 DHS	82	90

Note: 'Higher risk sex' refers to sex with a non-marital, non-cohabiting partner. Blank cells represent missing data. Data accessed on May 24, 2017 through the StatCompiler tool available from the Demographic and Health Survey project at <http://www.statcompiler.com/en/>.

The multipliers on the probability of infection per act (MC, C, PrEP and ART) are based on the probability of circumcision, condom, PrEP or ART use and the effectiveness of each in preventing the transmission of HIV. Effectiveness rates used in this analysis are 0.6 for male circumcision<sup>10–12</sup>, 0.8 for condoms<sup>3</sup>, 0.8 for PrEP<sup>13–16</sup> and 0.95 for ART<sup>17</sup>. The probability of infection per act and the STI and stage of infection multipliers are selected from within published ranges to best fit the epidemic in each country. Ranges are 0.0008 – 0.0016 for the probability of infection per act<sup>18,19</sup>, 2–11 for STIs<sup>20,21</sup>, 0.8–44 for primary stage infection<sup>22–24</sup> and 4–12 for symptomatic stage infection<sup>22</sup>. The number of contacts per partner and the number of partners per year are exponents in the equation to convert the risk per act into a cumulative risk of infection across all acts and all partners. Condom coverage represents the percentage of sexual acts that involve condom use. Since the model does not track individuals separately, it does not distinguish between consistent and inconsistent use. Each condom used has the effect of reducing the probability of transmission for that act. The cumulative impact across all acts is the net effect of condom use<sup>7</sup>.

We applied the Goals model to 77 countries that together account for 94% of new infections globally in 2019 (<https://aidsinfo.unaids.org/>) and then scaled-up the result to correspond to the global epidemic. The full list of countries included is in *Underlying data*<sup>8</sup>. The model is implemented for each individual country by using country-specific data for demographic indicators (base year population, fertility, mortality, and migration) (<https://population.un.org/wpp/>), behavioral indicators (number and type of partners, condom use) from national household surveys (<https://www.statcompiler.com/en/>), and HIV program data (number of people on ART and number of women receiving prophylaxis to prevent mother-to-child transmission (PMTCT) and number of male circumcisions) (<https://aidsinfo.unaids.org/>). The model is fit to data on prevalence from surveys, surveillance, and routine testing by varying the epidemiological parameters within published ranges. The ranges used for the epidemiological parameters and the fitted values by country are provided in the underlying data. Historical trends in condom use

by population group were estimated from self-reported condom use in DHS. Reported condom use in commercial sex was used for sex worker contact, reported use among those engaging in higher-risk sex was used for those with multiple partners and reported condom use for contraception was used for those with one partner. Information on the size of key populations is from the UNAIDS Key Population Atlas (<https://kpatlas.unaids.org/>).

Once the model was fit to each country's actual epidemic we conducted three analyses: (1) a retrospective analysis that estimates the number of additional HIV infections that would have happened if condom use rates stayed constant from 1990 to 2019, (2) a prospective analysis that compares the number of new HIV infections expected to occur between 2020 and 2030 if condom use rates remain at 2019 levels or increase to reach UNAIDS targets of 95% of casual and sex work contacts protected by condom use by 2025, and (3) a prospective analysis that compares constant condom use rates from 2019 to 2030 with a future where all key HIV interventions increase to UNAIDS targets by 2030<sup>15</sup> for key populations (sex workers, MSM, PWID, transgender people and prisoners), adolescent girls and young women, adolescent boys and young men, adults aged 25+, HIV-positive pregnant women and people living with HIV. Comprehensive services are targeted to the appropriate populations and include testing, treatment, condoms provision, needle and syringe exchange, opioid substitution therapy, PrEP, PEP comprehensive sexuality education, economic empowerment, voluntary medical male circumcision and prevention of mother-to-child transmission. These scenarios are illustrated in [Table 2](#).

We tested the sensitivity of the model results to the assumed effective of condoms in averting HIV infection by also running simulations with the effectiveness of condoms set to the low end of the 95% confidence interval (0.50) and with the high end (0.94).

## Results

According to UNAIDS estimates, the annual number of new HIV infections worldwide increased to a peak of about 2.8 million

**Table 2.** Scenario descriptions.

Scenario	Condom coverage	Coverage of other prevention interventions
Retrospective: 1990–2019		
- Counterfactual	Constant at 1990 levels	Actual
- Actual	Actual	Actual
Prospective: 2020–2030		
- Counterfactual	Constant at 2019 levels	Constant at 2019 levels
- Condom scale-up	95% of casual and sex work contacts protected by condoms by 2025	Constant at 2019 levels
- UNAIDS targets	95% of casual and sex work contacts protected by condoms by 2025	Scale up to all UNAIDS targets by 2025

around 1998 and then declined to 1.7 (1.2 – 2.2) million by 2019<sup>26</sup>. Model simulations with no increase in condom use rates after 1990 project that the annual number of new HIV infections would have increased to nearly 11 million by 2019 (Figure 1).

The difference between the lines represents 117 million infections averted from 1990–2019 due to increased condom use. Without the condom scale-up the cumulative number of new infections would have been 160 percent larger. About 45% of the estimated infections averted are in sub-Saharan Africa, 37% in Asia and the Pacific, 10% in Latin America and the Caribbean and 4% each in the Eastern Europe and Central Asia region and the Western and Central Europe and North America region. Impact for each of the modeled countries is shown in the *Underlying data*<sup>8</sup>. The largest absolute impacts, in terms of infections averted, are seen in the countries with the largest populations or highest prevalence (South Africa, India, China, Kenya and Tanzania) while the highest relative impact occurs in countries with low burden currently where condom use helped to avert a larger epidemic (Guatemala, China, United Kingdom, Italy, Mongolia and Bangladesh).

The sensitivity analysis of condom effectiveness indicates that the estimate of 117 million infections averted could be as low as 70 million or as high as 130 million.

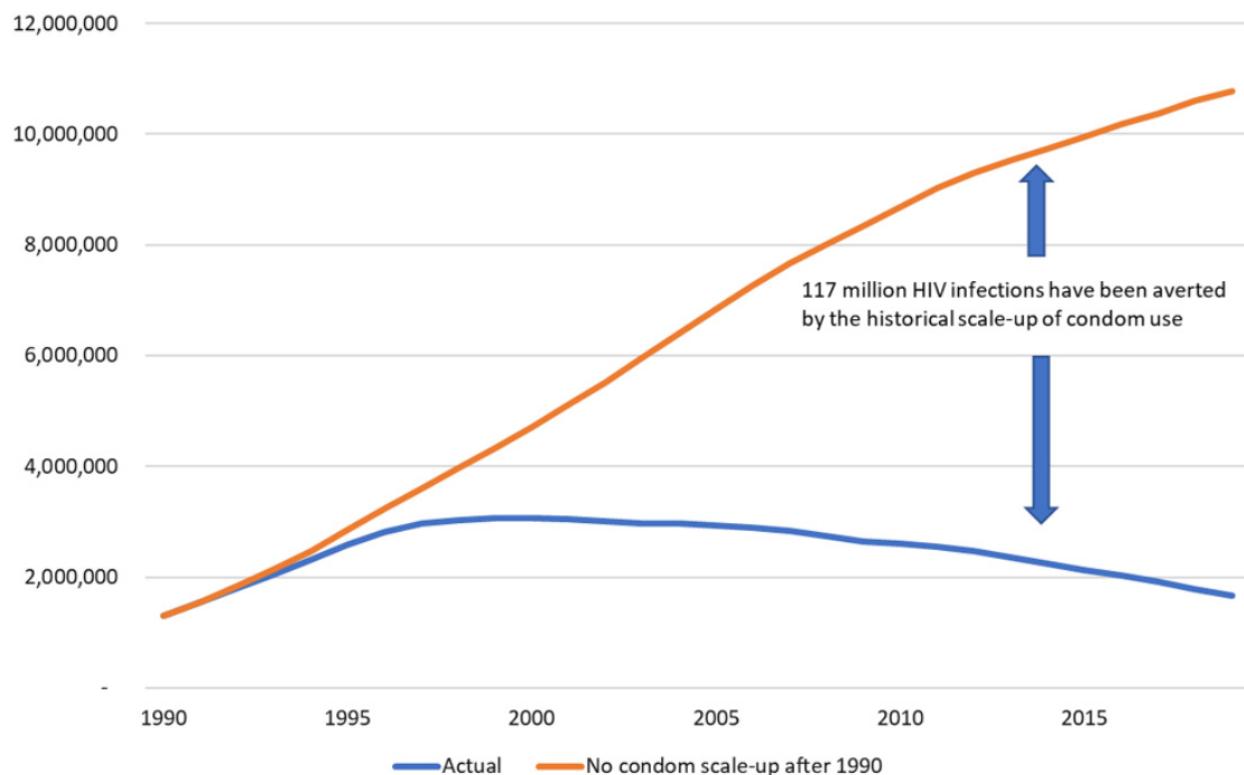
We do not know how many condoms were used globally between 1990 and 2019 but if we assume that condom use was very low in 1990 and scaled up to near today's rates by 2010

and remained approximately constant from 2010 to 2019, then total condom consumption for HIV prevention would have been around 160 billion for that period. This implies a global average of about 1300 condoms per infection averted. At an average cost per condom distributed of about \$0.18<sup>27</sup> the cost per infection averted by condoms during 1990–2019 is about \$230.170

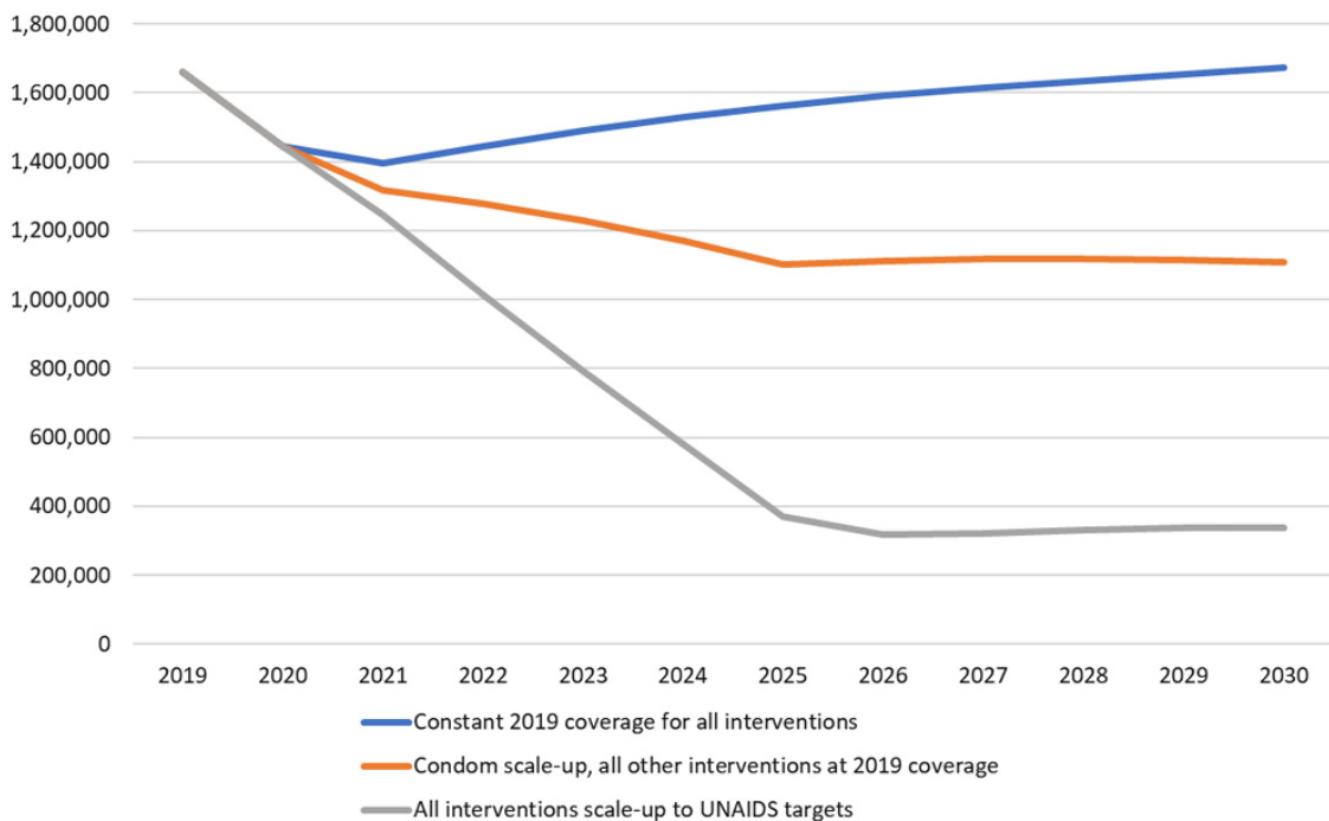
Figure 2 shows the two projections from 2019 to 2030. If condom use rates remained at their 2019 levels and all other interventions also had constant coverage, then the annual number of new HIV infections would rise slowly due to constant incidence and a growing population. If condom use rates scaled-up everywhere to the UNAIDS target of 95% of all risky sex acts and all other prevention interventions remained at 2019 coverage levels, then the number of new infections would decline to 1.1 million 2030. The difference between these two lines indicates that condom scale-up would avert about 3.6 million HIV infections over that period, about 20% of those that would occur without condom scale-up. Figure 2 also shows that the rapid scale-up of condom use could produce about one-third the impact as the full UNAIDS strategy, which scales up all the intervention mentioned above to UNAIDS targets.

## Discussion

Condom use has increased dramatically since the beginning of the HIV epidemic. Today, approximately 16 billion condoms are used annually to prevent infections and unintended pregnancies. Condom use has impacted the HIV epidemic and avoided a much worse HIV epidemic than has actually evolved.



**Figure 1. Number of new HIV infections with and without historical scale-up of condom use.**



**Figure 2. Number of new HIV infections in the future under three scenarios.**

Condoms can play a key role in future efforts, such as the Fast-Track initiative to end AIDS as a public health threat by 2030<sup>28</sup>.

The number of HIV new infections under the retrospective counterfactual scenario of no increase in condom use after 1990, which reaches 11million by 2019, is quite high compared to the actual level of about 1.7 million. But this just illustrates the benefits of early intervention. Early increases in condom use among key populations, in particular sex workers and their clients, as well as with non-regular partners has slowed early transmission and helped to avert a much larger epidemic in the general population.

There are several limitations to this analysis. We rely on self-reports of condom use in national surveys that may over-state actual use. The effectiveness of condoms depends on correct and consistent use but measures of these factors are not well developed. Our modeling estimates the impact of condom use in aggregate population groups but does not model individual behavior. Using these data our models can replicate historical epidemic trends in the countries modeled but that does not ensure that they are correct. Findings of this analysis are, however, broadly consistent with other mathematical modelling analyses of the impact of condom use<sup>29,30</sup>. Estimates of the size of key populations in each country are based on small sample surveys which may not be representative of the entire country. Estimates of the number of acts per partner are based on small

studies or potentially unreliable self-reports. To some extent, these limitations are addressed by fitting the model to historical data on prevalence. While the fitting does not guarantee that all the inputs are correct, it does ensure that the set of inputs is sufficient to replicate the historical epidemic. In spite of above-mentioned limitations, the case for the importance of condoms as an ongoing component of HIV programming is compelling.

Previous modeling studies have shown the impact of historical condom scale-up in specific populations in specific-countries including sex workers in Benin<sup>31</sup> and MSM in Beijing, China<sup>32</sup>. Other studies have modeled the potential impact of programs to scale-up condom use, including adolescents in the United States<sup>33</sup> and hypothetical but representative settings<sup>34</sup>. All found significant impacts of condom use, but none examined the global impact. Condoms are a good investment. The total cost to prevent one new HIV infection with condoms is small compared to life-time costs of treatment meaning that condom investments now will save future expenditures on treatment. Since many people rely on free or subsidized condoms, it is crucial to ensure adequate funding for condom programs, including demand creation activities and frequent behavioral data collection.

While condoms are not a magic bullet that alone can control the HIV epidemic, they remain a critical part of the prevention response. Scale-up of condoms use is a necessary component to

reach the UNAIDS global targets<sup>9</sup> and any reduction in support for condoms would seriously affect the chances of achieving those targets. Unfortunately, support for condom social marketing programs has been decreasing in recent years<sup>35</sup>. International and domestic financing should continue to support general population condom programs even as new technologies are introduced that are targeted to the highest risk populations. Condom programs remain among the most cost-effective interventions in the response and provide other health benefits including prevention of other sexually transmitted infections and protection against unwanted pregnancies<sup>1</sup>. Past experience has shown that we do know how to promote and distribute condoms and that many people will use them if they're available. Recent declines in condom investments especially around demand creation implies that the younger generation have not been exposed to relevant condom promotion and condom use skills, a worrisome trend given the relative size of young populations in low- and middle-income countries.

## Data availability

### Underlying data

Zenodo: JGStover/Data-for-condom-impact-paper-on-Gates-Open-Research: Impact of condoms. <https://doi.org/10.5281/zenodo.4898086><sup>8</sup>.

This project contains the following underlying data:

- Appendix Table 1.csv (number of new HIV infections by country from 1990–2019 according to actual trends

or a counterfactual scenario in which rates of condom use remain at 1990 levels)

Zenodo: JGStover/Data-for-condom-impact-paper-on-Gates-Open-Research: Impact of condoms. <https://doi.org/10.5281/zenodo.4898086><sup>8</sup>.

This project contains the following extended data:

- Parameter ranges used for model fitting.docx (the ranges for key epidemiological factors used in model fitting)
- Fitted parameter values by county.docx (final fitted values for key epidemiological parameters for each country)
- Calculation code (the Delphi code for the simulation calculations in the Goals in .PAS format)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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35. Smith B, Mann C, Jones C, et al.: **Challenged and Recommendations for Reaching “Fast-Track” Targets for Condom Use.** Mann Global Health, 2019.  
[Reference Source](#)

## Open Peer Review

Current Peer Review Status:  

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### Version 2

Reviewer Report 18 March 2022

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Akira Shibanuma 

Department of Community and Global Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Thank you very much for addressing the comments made in the previous round. The following is a minor comment related to the comment made in the previous round.

**Response:** We do provide a citation for the full model details when we say 'Complete model details are available elsewhere [24]'. That reference provides equations and data sources. This is the same model used in the PLoS Medicine paper. We have added a citation to the PLoS Medicine paper to make that clear. We have also added some clarification to the use of the number of acts per partner and the number of partners as exponents in the equation.

Regarding the response to the reviewer above, I could not find the description ('Complete model details are available elsewhere [24].') in the version 1 of the manuscript. I understand that what the authors used in this manuscript is the Goals RSM (Risk-Structured Model) used in the Plos Medicine paper by the authors (Ref number 9 in the current version of the manuscript), and that the model detail was described in the web appendix of the author's different paper (Ref number 7). If this understanding is correct, the authors might want to clarify it in the manuscript for readers' better understanding of the model.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** community health; health promotion; maternal, newborn, and child health; immigration and health; prevention and control of infectious diseases

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 25 February 2022

<https://doi.org/10.21956/gatesopenres.14833.r31759>

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✓ **Innocent Modisaotsile**

United Nation Population Fund, UNFPA, New York, NY, USA

**Willis Odek**

UNFPA, New York, NY, USA

Thanks a lot for sharing with us the latest version. We have reviewed it and we think our observations were adequately addressed. We therefore approve the paper without any reservations.

**Competing Interests:** No competing interests were disclosed.

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Version 1**

Reviewer Report 05 November 2021

<https://doi.org/10.21956/gatesopenres.14517.r31288>

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? **Akira Shibanuma** 

Department of Community and Global Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

This study developed a mathematical model for the incidence of HIV infection in 77 high HIV burden countries to estimate the difference in the incidence between the cases of the actual and hypothetical condom coverage among risk populations of HIV infection. This prevalence highlights the importance of promoting condom use among these populations. I hope the following points would help the authors update the manuscript.

1. Model: This manuscript does not describe the model in detail, unlike a modelling paper published by the authors (e.g., the PloS Medicine paper <sup>1</sup>). The model for the incidence in

the present study seems to differ substantially from the one in the PloS Medicine paper (Function (2) in S2 Text) (of course, the purpose of the modelling differed, too). Note that readers in this journal are not necessarily familiar with modelling studies. For example, readers may want to know different roles of  $\text{Prev}_{s',r,t} \times (1-r_s \times S_{s,r,t} \times \text{STI}_{s,r,t} \times \text{MC}_t \times C_{r,t} \times \text{PrEP}_{s,r,t} \times \text{ART}_{s,r,t})^a$  and  $(1 - \text{Prev}_{s',r,t})$ , reasons of using exponential functions with regard to the number of acts per partner and the number of partners. Although there is no citation for the model, the authors may want to add references if the model in the current study was built based on previous works.

2. Values to be input in the model: The authors may want to describe how values of several key variables were obtained, such as the coverage of condom use among each of risk populations in 1990 and onward in each country, the estimated number of these key populations in the past, present, and future years. The authors may want to describe assumptions in the estimated values, if any, in the Methods section and in the limitations in the Discussion section. In addition, values that were input in the model may need to be attached so that readers can verify the validity of the modelling.
3. Sensitivity analysis: For future estimations, the authors may need to consider sensitivity analysis for different parameters and the past and future values of key variables. For example, it may not be realistic to have fixed values for the number of acts per partner and the number of partners among different key populations in the past or future years. In some countries, it may be difficult to obtain reliable sources for the current statistics for these numbers.
4. Discussion: The discussion section does not contain the interpretations of findings, comparisons of findings in this study with ones in previous studies, and implications for the global targets related to HIV/AIDS.

## References

1. Stover J, Glaubius R, Teng Y, Kelly S, et al.: Modeling the epidemiological impact of the UNAIDS 2025 targets to end AIDS as a public health threat by 2030. *PLoS Med.* **18** (10): e1003831 [PubMed Abstract](#) | [Publisher Full Text](#)

## Is the work clearly and accurately presented and does it cite the current literature?

No

## Is the study design appropriate and is the work technically sound?

Yes

## Are sufficient details of methods and analysis provided to allow replication by others?

No

## If applicable, is the statistical analysis and its interpretation appropriate?

Partly

## Are all the source data underlying the results available to ensure full reproducibility?

No

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** community health; health promotion; maternal, newborn, and child health; immigration and health; prevention and control of infectious diseases

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 04 Feb 2022

**John Stover**, Avenir Health, Glastonbury, USA

Reviewer #2

**Akira Shibanuma**, Department of Community and Global Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

This study developed a mathematical model for the incidence of HIV infection in 77 high HIV burden countries to estimate the difference in the incidence between the cases of the actual and hypothetical condom coverage among risk populations of HIV infection. This prevalence highlights the importance of promoting condom use among these populations. I hope the following points would help the authors update the manuscript.

- Model: This manuscript does not describe the model in detail, unlike a modelling paper published by the authors (e.g., the PLoS Medicine paper [1](#)). The model for the incidence in the present study seems to differ substantially from the one in the PLoS Medicine paper (Function (2) in S2 Text) (of course, the purpose of the modelling differed, too). Note that readers in this journal are not necessarily familiar with modelling studies. For example, readers may want to know different roles of  $\text{Prev\_s}',r,t \times (1-r_s \times S_s,r,t \times STI_s,r,t \times MC_t \times C_r,t \times PrEP_s,r,t \times ART_s,r,t)^a$  and  $(1 - \text{Prev\_s}',r,t)$ , reasons of using exponential functions with regard to the number of acts per partner and the number of partners. Although there is no citation for the model, the authors may want to add references if the model in the current study was built based on previous works.

**Response:** We do provide a citation for the full model details when we say 'Complete model details are available elsewhere [24]'. That reference provides equations and data sources. This is the same model used in the PLoS Medicine paper. We have added a citation to the PLoS Medicine paper to make that clear. We have also added some clarification to the use of the number of acts per partner and the number of partners as exponents in the equation.

- Values to be input in the model: The authors may want to describe how values of several key variables were obtained, such as the coverage of condom use among each of risk populations in 1990 and onward in each country, the estimated number

of these key populations in the past, present, and future years. The authors may want to describe assumptions in the estimated values, if any, in the Methods section and in the limitations in the Discussion section. In addition, values that were input in the model may need to be attached so that readers can verify the validity of the modelling.

**Response:** We have added a description of the sources of information on historical condom use and the estimation of key population sizes. Table 1 shows the reported condom use rates by population group and country.

- Sensitivity analysis: For future estimations, the authors may need to consider sensitivity analysis for different parameters and the past and future values of key variables. For example, it may not be realistic to have fixed values for the number of acts per partner and the number of partners among different key populations in the past or future years. In some countries, it may be difficult to obtain reliable sources for the current statistics for these numbers.

**Response:** Yes, we agree that these inputs are not well known and have added some text in the limitations paragraph to acknowledge this.

- Discussion: The discussion section does not contain the interpretations of findings, comparisons of findings in this study with ones in previous studies, and implications for the global targets related to HIV/AIDS.

**Response:** We have added comparisons to four other studies and expanded the discussion to include implications for the global targets.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 01 July 2021

<https://doi.org/10.21956/gatesopenres.14517.r30763>

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## Innocent Modisaotsile

United Nation Population Fund, UNFPA, New York, NY, USA

## Willis Odek

UNFPA, New York, NY, USA

This study presents a retrospective (since 1990) and prospective (up to 2030) analysis of the role of condoms in averting new HIV infections using the Goal Model in 77 countries. The model parameters are clearly spelled out and justified. The analysis uses data collected through representative general population surveys. While the analysis focuses on the role of condoms in averting new HIV infections, it also models the effect of other HIV prevention interventions on new HIV infections. We were concerned upfront about the accuracy of condom use estimates from

general population surveys, but this limitation has been duly acknowledged by the authors and reflected in the interpretation of results with a caveat that the analysis does not measure consistent condom use, which is a behavioral factor.

It would be helpful to clarify or elaborate further on the following:

1. The rationale for setting the baseline analysis period to 1990, especially given the emergence of new HIV prevention tools, including ART, and their roll out to most affected countries only towards the year 2000.
2. The formula for estimating the probability of becoming infected in a year includes a parameter on HIV prevalence of the opposite sex. Considering that in many regions, gay men and men who have sex with men contribute significantly to new infections (64% in West and central Europe, 44% in Asia and the pacific as well as Latin America – source: 'UNAIDS 2021, Global Commitment, Local Action - After 40 years of AIDS, charting a course to end the pandemic' (link to source available [here](#)) - how did we address this parameter?
3. The paper also indicates that private sector contributes 60% of condoms in at least 55 countries based on DHS. While this might be a global average, for other regions such as sub-Saharan Africa, the major contributor is the public sector, with the private sector contributing less than 20%. It might be worth noting the exceptions, especially given the importance of free condoms in the African continent..

Given its estimation of some 117 million new HIV infections averted since 1990 due to scale up of condom use, the paper should include a strong programmatic recommendation for effective integration of condom programming with other HIV prevention interventions, including sexual and reproductive health and rights.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**We confirm that we have read this submission and believe that we have an appropriate level**

**of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.**

Author Response 04 Feb 2022

**John Stover**, Avenir Health, Glastonbury, USA

Reviewer # 1

**Innocent Modisaotsile**, United Nation Population Fund, UNFPA, New York, NY, USA

**Willis Odek**, UNFPA, New York, NY, USA

This study presents a retrospective (since 1990) and prospective (up to 2030) analysis of the role of condoms in averting new HIV infections using the Goal Model in 77 countries. The model parameters are clearly spelled out and justified. The analysis uses data collected through representative general population surveys. While the analysis focuses on the role of condoms in averting new HIV infections, it also models the effect of other HIV prevention interventions on new HIV infections. We were concerned upfront about the accuracy of condom use estimates from general population surveys, but this limitation has been duly acknowledged by the authors and reflected in the interpretation of results with a caveat that the analysis does not measure consistent condom use, which is a behavioral factor.

It would be helpful to clarify or elaborate further on the following:

- The rationale for setting the baseline analysis period to 1990, especially given the emergence of new HIV prevention tools, including ART, and their roll out to most affected countries only towards the year 2000.

**Response:** While the scale-up of key programs such as ART, PMTCT and VMMC only took place after 2000, increases in condom use started much earlier. In the 1990s programs focused on ABC (Abstinence, Be Faithful and Condoms). We wanted to capture the full benefits of increases in condom use by starting the analysis in 1990.

- The formula for estimating the probability of becoming infected in a year includes a parameter on HIV prevalence of the opposite sex. Considering that in many regions, gay men and men who have sex with men contribute significantly to new infections (64% in West and central Europe, 44% in Asia and the pacific as well as Latin America – source: 'UNAIDS 2021, Global Commitment, Local Action - After 40 years of AIDS, charting a course to end the pandemic' (link to source available [here](#)) - how did we address this parameter?

**Response:** Thank you for catching that. The formula actually uses prevalence in the partner population whether the partner is the opposite or same sex. We have revised the variable description to show that.

- The paper also indicates that private sector contributes 60% of condoms in at least 55 countries based on DHS. While this might be a global average, for other regions such as sub-Saharan Africa, the major contributor is the public sector, with the private sector contributing less than 20%. It might be worth noting the exceptions, especially given the importance of free condoms in the African continent.

**Response:** We have updated the text to include the latest data from DHS and social marketing which indicate that 60-70% of those using condoms for contraception get them

from public sources and social marketing accounts for nearly 2 billion condoms each year.

- Given its estimation of some 117 million new HIV infections averted since 1990 due to scale up of condom use, the paper should include a strong programmatic recommendation for effective integration of condom programming with other HIV prevention interventions, including sexual and reproductive health and rights.

**Response:** We feel that we do make a strong recommendation for continued support for condom programming in the last paragraph of the discussion.

**Competing Interests:** No competing interests were disclosed.

# Treatment ‘cultures’, sexually transmitted infections and the rise of antimicrobial resistance

Shiva Chandra<sup>1</sup>  | Alex Broom<sup>1</sup> | Damien Ridge<sup>2</sup>  | Michelle Peterie<sup>1</sup> | Lise Lafferty<sup>3,4</sup> | Jennifer Broom<sup>5,6</sup> | Katherine Kenny<sup>1</sup>  | Carla Treloar<sup>4</sup> | Tanya Applegate<sup>3</sup>

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## Abstract

In this article, we examine the current management of sexually transmitted infections (STIs), in the context of rising antimicrobial resistance (AMR), through the lens of ‘treatment cultures’. Prevailing treatment cultures—including the prominence of syndromic care for STIs—foster certain possibilities and foreclose others, with important consequences for countering AMR. Drawing on qualitative interviews with STI professionals, experts and industry representatives, we unpack these stakeholders’ accounts of STI treatment cultures, drawing out the importance of *socio-historical* (i.e. taboo and stigma), *political-economic* (i.e. perceptions of significance, profit-making and prioritisation) and *subjective* (i.e. patient contexts and reflexivity) dimensions therein. In developing this critical account of how treatment cultures are formed, reproduced and indeed resisted, we reveal how such discourses and practices render the reigning in of AMR and shifting antibiotic use difficult, and yet, how productive

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engagement remains key to any proposed solutions. As such, the article contributes to our understanding of AMR as a highly diversified field, through our exploration of the bio-social dimensions of resistance as they relate to the case of STIs.

**KEY WORDS**

qualitative research, sexual health, sociology of antimicrobial resistance, sociology of care

## INTRODUCTION

Bacterial sexually transmitted infections (STIs) have received comparatively little attention relative to other areas in which antimicrobial resistance (AMR) is a growing concern (Seña et al., 2020; Williamson & Chen, 2020). Yet, STIs have widespread impacts, which are worsening as antibiotics become less effective (Unemo et al., 2017). It is estimated that one million STIs are acquired every day across the world, with 129 million cases of chlamydia, 82 million cases of gonorrhoea and 7.1 million incidents of syphilis documented internationally each year (WHO, 2023b). There has been a lack of interest, political will or economic investment to proactively engage in rising resistance for STIs. While HIV, with associated high mortality and societal costs, has been a focus of significant investment, innovation and subsequent drug development, bacterial STIs have languished in the cultural shadows (WHO, 2012; WHO, 2021). This is, as our participants reflect on below, in part due to enduring sexual taboos (Lichtenstein, 2003; Nesamoney et al., 2022) and perceptions of STIs being ‘less serious’ than other illnesses. Yet, a cliff edge is nearing with rising resistance, and in particular, serious concerns raised about AMR in *Neisseria gonorrhoeae* (gonorrhoea) and *Mycoplasma genitalium* (Iwuji et al., 2022; WHO, 2023a).

Here, drawing on a series of interviews with clinical, expert and industry stakeholders, we examine STIs resistance and the aligned problem of antibiotic ‘overuse’, to explore their views on how prevailing ‘treatment cultures’ emerge and sustain themselves, and their implications for rising rates of resistance. This is placed within a broader scene whereby sexual health practitioners are being asked to be increasingly judicious with antimicrobials (Kenyon et al., 2023; Tompson & Chandler, 2021) to kerb resistance.

The idea of ‘treatment cultures’, we argue below, is instructive for advancing the sociology of AMR, which has already done considerable work to explore the phenomena of resistance beyond mere biology, or individual or practitioner decision-making (e.g. Adam et al., 2020; Broom et al., 2017; Broom et al., 2021; Broom et al., 2023; Chandler, 2020), to explore its embeddedness in structural fragilities, economic priorities and cultures of immediacy, among many other bio-social forms (Will, 2018; see also Brown & Nettleton, 2017b on resistance imaginaries). Thinking with a ‘cultures’ frame provides an abstraction to help make sense of how bio-social forms assemble modes of practice.

It also remains that thus far, little of the sociological AMR scholarship has touched on STI related issues, which as a case study and site of sociality throws up unique dimensions which are instructive for the broader scene of AMR. This includes contours of stigma and taboo,

interplaying, as they do, with ideas about severity, responsibility and forms of cultural (de) prioritisation. Moreover, an exploration of the perception of treatment cultures within such a context, sheds light on the tussle between normative influences, interpersonal desires to ameliorate illness and provide care, whilst concurrently pursuing efforts to curb AMR.

## BACKGROUND

### Epistemologies of STIs

The 'successes' of antimicrobial treatments for STIs have, to some extent, given rise to a critical paradox. As new antibiotics were introduced over the decades to treat gonorrhoea, for example, these treatment 'successes' have subsequently become 'failures' in their ability to cure the disease due to rising rates of AMR. In other words, initial successes of antimicrobials have diminished in their returns over time. In the 1930s, sulfonamides were used to treat gonorrhoea infections, but by the late 1940s more than 90% of gonococcal isolates showed resistance to sulfonamides, leading to a replacement of the treatment with penicillin (Jose et al., 2020; Unemo & Shafer, 2014; Workowski et al., 2008). However, resistance to penicillin was emerging as early as 1946 (Jose et al., 2020). This saw the introduction of chlortetracycline to treat penicillin resistant strains, which led to the emergence of tetracycline resistance, and by the 1980s resistance to penicillin and tetracycline meant azithromycin and fluroquinolones became preferred modes of treatment (Unemo & Shafer, 2014; Workowski et al., 2008). In the 1990 and 2000s, resistance to azithromycin in European countries, the United States and Argentina meant it was no longer used as a single dose treatment for gonorrhoea (Unemo & Shafer, 2014). Increasing resistance to fluroquinolones during the 2000s saw this class of antibiotics also being abandoned in European and Asian countries (Unemo & Shafer, 2014). Cephalosporins, such as ceftriaxone and cefixime have been used since the 1990s, however, as a result of increasing concerns about resistance (CDC, 2021), combination antimicrobial treatment (ceftriaxone and azithromycin) is now the standard of care. However, this approach results in antibiotic resistance pressure for other organisms such as *Mycoplasma genitalium* and non-STI enteric pathogens, and some countries have moved away from the combination antimicrobial approach for this reason (CDC, 2021).

While this narrative may appear to be about unfortunate biological processes, this is a partial account, with swiftly rising resistance embedded in societal processes including the perception of microbes, economic and political priorities, misuse of resources and critically, prevailing notions of 'appropriate treatment' (Andraka-Christou, 2020; Baccini et al., 2022; Sell & Williams, 2020). This is evident in the multitude of strains of thought, and frameworks, for making sense of STIs (Aral, 2002; Crosby et al., 2016). Kenyon (2020) and Kenyon et al. (2022) broadly differentiate between these as individualist vis-à-vis ecological epistemologies for understanding STIs. They argue that the former tends to focus on intensive screening, eradication of microbes and individual characteristics and behaviours of people, while the latter focuses on contexts, interdependencies and multi-level analysis. Whilst there is an intermingling of viewpoints (Kenyon, 2020), enduring divisions still permeate the STI milieu. The influence of epistemological framings, such as individual versus ecological, shapes the way diseases are perceived, prioritised and ultimately treated. For example, an individualist framework will place emphasis on a disease and its elimination through antibiotics, whilst an ecological framework opens greater space for considerations about how these antibiotics affect other aspects of a person's

health, or the importance of stewardship (Kenyon et al., 2022). This points to how treatment, often deemed to be the appropriate and ‘medico-scientific’ approach, turns out to be a cultural formation, sometimes enacting longer term harm, and therefore open to reflexivity, interrogation and transformation. We argue that such deliberations are critical to dealing with the current threat of antibiotic resistant STIs.

## STI care through a ‘cultures’ lens

Building on the accounts of our participants shown below, here we focus on ‘treatment cultures’, as an important context for engaging with the presence and problem of resistance (Jenks, 2005).<sup>1</sup> The turn towards viewing practice-as-culture may seem like a rather pedestrian notion, yet as social scientists have shown across multiple sites and contexts (Armstrong, 1995; Good & Hannah, 2010; Kleinman et al., 1978; Mol, 2002, 2008), such a framing has the potential to better illuminate complex and contingent practices such as antibiotic use by highlighting hitherto hidden values, prevailing epistemologies and the highly selective ontologies at the intersection of bugs, bodies and intervention. That is, a ‘culture’ framing means paying attention to how science and medicine, in this case of and around STIs, *constructs* the objects/subjects it seeks to intervene upon, thus foregrounding and foreclosing the potential actions that can be taken in relation to them and how these normative forces may also be troubled, resisted and revised by those responsible for delivering care.

Connecting with the ecological framework raised above (Kenyon et al., 2022), a cultures frame also fully links instances of intervention or treatment (i.e. testing for STIs or deployment of antibiotics) with their disparate and multidimensional personal, interpersonal and structural influences. This includes recognising that these multidimensional and entangled influences reach well beyond the clinic and into the realms of the multi-scalar, spanning organisations and public, private and corporate entities (Ecks, 2005; Fisher et al., 2015; Gagnon & Lexchin, 2008). Thus treatment cultures and aligned practices are always emergent at the interstices of culture, economy, expertise and evolving technologies. This also allows for the notion of different, plural, treatment cultures (within health systems, across nations, across spaces/locale and so on), acknowledging the multiple ways of *doing* STI care (WHO, 2016). Critically, seeing treatment as culturally co-produced, centres the multidimensional changes that need to take place (Tompson & Chandler, 2021), including how infection, antibiotics and care are thought about and the normative practices surrounding them.

As suggested, treatment cultures have normative, discursive and practical aspects, which circulate and are emergent over time and across contexts (Armstrong, 1995). Rather than still or set, treatment cultures evolve in relation to such things as technological change, management standards, evidence-making and communities of practice (Broom et al., 2017; Mol, 2008). They are never settled, but also, have normative, structuring aspects, which in context of this study assemble to create dominant modes of practice through routine, guidelines, ideas about ‘healthy’ bodies and available resources (see ASHM National Prep Guidelines, 2021). Moreover, because treatment cultures are always emergent, they are much about practices of treatment, as they are about reflections on these practises, which may challenge the need to treat all instances of infection itself (Armstrong, 2018).

In the context of this study, our understanding of the dominant treatment culture—as both normative force and everyday practice—emerges from the reflexivity of participants, and is located in their reflexive practices, in much the same way that for example, racism or sexism

(Ang et al., 2024; Chandra et al., 2024) may be elucidated by reflections and interventions to address them. This also means, participants identify features of the prevailing treatment culture, trouble parts of it and assemble their own ways of brokering professionalism, delivering care and trying to curb the rise of AMR, as we explore below.

## METHODS

### Sampling and data collection

This article draws on and extends our ongoing body of research, which examines the economic, social and political drivers of antibiotic resistance (e.g., Broom et al., 2021; Broom et al., 2023; Peterie et al., 2023), to unpack how prevailing social practices assemble to shape antibiotic resistance in the context of STIs. We present findings from qualitative interviews that were conducted from 2021 to 2023 with a diverse range of stakeholders with expertise in STIs and AMR. Stakeholders were recruited by purposively sampling through researcher networks, to ensure participants possessed the appropriate expertise required for the project. Data collection entailed in-depth, semi-structured interviews with stakeholders working to curb AMR in clinical, private sector and pan-national contexts. Participants ( $n = 23$ ; male = 10, female = 13) were comprised of sexual health clinicians and general practitioners, key industry stakeholders involved in pharmaceutical and/or diagnostic research and development, and representatives of peak pan-national organisations. All clinical participants ( $n = 13$ ) came from Australia. Participants representing industry and pan-national organisations held professional roles in Australia ( $n = 5$ ), Europe ( $n = 3$ ) and the US ( $n = 2$ ). As such, this study has a lean towards Australian experiences ( $n = 18$ ). Video conferencing was used to conduct interviews by authors Alex Broom, Michelle Peterie and Lise Lafferty. They ranged between 30 and 60 min. Interviews were audio-recorded and transcribed verbatim. This involved the removal of all identifying information to preserve participant confidentiality. Interview questions and discussions revolved around three key themes: participants' perceptions and direct experiences of AMR in the context of STIs, their ongoing efforts to develop and implement AMR solutions in their respective contexts, and support or challenges faced when working to do so. Key interview questions to illicit this information included: What are the main strategies currently used to ameliorate resistance in STIs, in your context? What do you see as the main (short, mid and/or and longer term) costs in terms of effects of resistant STIs? To what extent does AMR shape your practice in STI care, and has this changed over time? The study received ethics approval from the University of Sydney's Human Research Ethics Committee (reference: 2022/128). Informed consent was obtained from all interviewees who participated in the study in alignment with the approved ethics protocol.

### Data analysis

A framework approach was used to analyse the data in this study (Pope & Mays, 2006). This involved five key steps (1) Familiarisation: review of transcripts by members of the research team. (2) Identification: discussion within the research team to identify key themes that answered the research questions. (3) Application of themes: transcripts were coded thematically, which meant identifying key excerpts that reflected identified themes. These data were

also inductively organised into sub-themes. (4) Charting: an overall picture of the data was built using headings and sub-headings, which included sub-themes that had been identified in step 3. For this article in particular, charting sought to unpack how STI treatment in the context of AMR can be understood as a cultural production. (5) Mapping and interpretation: associations between data points were clarified and explanations developed and written.

The team decided thematic saturation had been reached once ideas and experiences new participants described in their interviews echoed ideas and experiences already documented in interviews (see Guest et al., 2020). Coding was undertaken by multiple team members, and analysis was shared and discussed with the wider research team, including clinician-researchers, to confirm the consistency and credibility of the interpretation, and to ensure consensus was reached about findings. Atypical, negative, conflicting and contradictory items were also identified during theme development and coding to enhance analytic rigour. However, the emphasis in this study has been to identify recurring and dominant themes within the dataset, and in this article, to understand how treatment can be conceptualised as a cultural production to understand STIs and AMR, including political and economic considerations, normative practices and conceptualisations of disease, and individuals' engagements with them, to develop a panoramic view of how change can take place. We will use quotes from interviews to illustrate key themes, and to support interpretation of the data.

## RESULTS

### The politics of treatment cultures

Whilst clinical interactions and exchanges may not always seem entangled in politics and economics, they inevitably are, shaping the potential of treatment cultures (Dixon et al., 2021). The limits and boundaries of possibility are very often induced or foreclosed outside of the clinic. Often weaving in cultural ideologies, and the undulations of secrecy and taboo in STIs, prevailing treatment cultures are at least partially assembled in policy decision-making, political blind-spots and/or practices of scientific deprioritising. As interviewees explained, the flows from political interest are strong and enduring, with the complex intersection of stigma, and the idea of 'undeserving' subjects creating a perfect storm for a lethargy of action to improve STI practices in relation to rising resistance. As one participant told us below:

It's not pleasant discussion to have with someone about syphilis and gonorrhoea and all of that. Politicians aren't interested, and it would be the brave politician that might take that on because, again, that would be seen as something a bit - it's not one of those things that people donate lots of money to [...] Children's research, endless money. STIs, no one's interested. No one wants to take that on ... I think there's a big assumption of, "Well, it serves them right. It's their fault that they've got this." There's a lot of blame associated with STIs over any other disease.

(Clinician, Australia)

Deservingness of attention and investment of resources was simultaneously tied to the perceived severity of STIs within the accounts of our participants. It was noted that whilst infections may cause suffering, '*there's not a lot of death*' [Industry, US]. While there has been some increase in interest in antibiotic resistant STIs—most notably in England due to media

attention about 'Super Gonorrhoea'—our participants considered their work, field and the concerns of communities impacted by STIs to be low on the political agenda. This has a potential impact on innovation, proactive policy and good governance (or lack thereof).

Ultimately, the prioritisation of STIs was talked about within the interviews as located within a prevailing cultural imaginary where stigma, personal responsibility and perceptions of severity heavily influence treatment, and treatment cultures, resulting in a relative paucity of resources being allocated to addressing antibiotic resistant STIs. This lack of prioritisation concurrently weaves through instances of care, significantly shaping treatment cultures, including the intersection of practice and innovation.

## The practice–innovation nexus

Whilst often beyond the view of interventions in the clinic, interviews revealed that scientific innovation, technological development and the limits of industrial production/distribution are integral to both assembling and developing treatment cultures, creating or foreclosing material possibilities (i.e., new drugs and new diagnostics). As such, broadening the lens within which STI care is viewed, shows how prevailing treatment cultures exist at the nexus of economical-social–political considerations.

The influence of these matters is evident, for instance, in the ongoing urgency for quicker and more accessible tests to be made available, to identify STIs (e.g., *Neisseria gonorrhoea*) and specific strains of STIs, allowing clinicians to provide faster and more exacting treatments as follows:

I think because we have a lack of point-of-care testing. So if we have a bedside test where we can do a point-of-care test and tell the patient that, "In 10–15 minutes we can give you a result, so we know whether to actually treat you for this condition or not." It's just that we don't have the lab technology. So, as a result of that, you've got a patient in front of you who's unwell, who's at risk of spreading it to other partners if not treated then and there. We are overtreating because we don't know what the causative organism is. Whereas if we had point of care testing, that way you can get an answer in real time, you'd be able to overcome that.

(Clinician, Australia)

So, having a specific mutation on a molecular test, similar to what they have for tuberculosis, this molecular testing for rifampicin and isoniazid-resistant tuberculosis, so you know quite quickly, initially, but then you should give first-line treatment or change the treatment. So, I think something like that would be great for sexual health while you're balancing the need to treat quickly versus trying to target your treatment appropriately.

(Clinician, Australia)

These material possibilities—and, indeed, current technological limitations—are imbricated with and emerge from financial viabilities, and politically driven cost-benefit considerations. They are also connected with the flailing pipeline of drug and diagnostic innovation, which is deeply interconnected with public sector priorities (see Peterie et al., 2023). Put differently, what happens in the clinic is embedded in dimensions of the economy of health and care,

incorporating the flow-on effects of the priorities of businesses (return on investment assessments), the ‘nudges’ of governments (subsidies) and so on:

My commercial counterparts are basically saying, “well I get it, there’s a medical need for it. But how much are you going to sell? And how much can we charge? How much is a customer going to pay?”

(Industry, US)

Has to be an element of risk sharing, I guess, with both governments, health services, and industry. I think it has to be a kind of a tri-party thing. Otherwise it’s hard for organisations to take the risk when they are responsible for losing, they have the most to lose. [...] If there’s no commitment, if we bring something to market and we trial it, it’s successful, but then we have to spend six years to try and get it into guidelines and reimbursement [from government] that’s a lot of time, that’s a lot of resources for us to commit with no certainty that we’re going to get any business after we get that.

(Industry, Australia)

As these quotes show, and as indicated by others we interviewed, the upstream conditions and decisions of industry, and the incentive structures of governments and policy makers, are influential in what technology makes it through to the clinic as a site of care. This demonstrates the processual nature of STI care, where porous and open-ended boundaries (Mol, 2008), between governance, priority setting and innovation investment impact what is possible in terms of streamlining and improving care, including the use of antimicrobials. Very often, treatment decisions are made in the context of *absence*—the absence of progressive policies, well thought through subsidy structures, swift low-cost innovations and so on. Upstream decisions, as articulated in the interviews, were viewed as generative of practices (including antimicrobial (mis) use), which often develop in the context of poor or absent resources and infrastructure. These all subsequently shape and produce treatment cultures, and exist alongside ongoing normative clinical practices, such as disease elimination.

## Culturing the clinic: Presumptive histories

The political, economic and innovation considerations surrounding STI treatment cultures—those mentioned above and beyond—coalesce with, and assemble, a routine, normative and taken-for-granted clinical practice. One challenging aspect of prevailing treatment cultures in the STI field (and infection care more broadly) is the practice of syndromic care—treatment based on signs and symptoms rather than definitive tests which certain participants believe is contributing to AMR. As a participant stated below:

For example, when somebody comes in with, say, proctitis, we treat them syndromically for all the organisms because they’re in a lot of pain and they want treatment at that point, but we’re treating many organisms over a period of time without having a diagnosis, without having a cause for that condition. So, I think that is also contributing [to AMR].

(Clinician, Australia)

Syndromic care has a temporal dimension, in that syndromic interventions, and associated cultures of practicing in this way, are deeply embedded not only historically, but also contemporarily, in the context of STIs. Signs and symptoms of infection may be *enough* to warrant swift pharmaceutical intervention. Additionally, the notion of a 'natural' recovery (more on this below) is largely unexplored in prevailing STI treatment cultures, with the STI perceived as a danger to be swiftly eliminated (albeit a possibility that may not always be available with the rise of AMR). In other words, syndromic care exists alongside the accumulated possibilities of technology and intervention, *making sense* within the logics of the prevailing treatment culture, but giving rise to potentially greater opportunities for resistance. As one interviewee stated below:

So, AMR is often not the priority for the clinician and the patient at the coal face, and it is invisible to them, and that the damage that they are doing is invisible. It's very like driving your car and catching your plane, you don't see that impact really or relate that impact directly to climate change or losing antibiotics [...] So I think it's education, is about making it more visible, very present in people's consciousness, understanding the longer term implications of short term practices...

(Clinician, Australia)

The temporal myopia (see Broom et al., 2021) and lack of visibility of consequences-at-scale (see Davey et al., 2017), which foreground treatment in the here and now, do little to connect to envisaged futures, since they focus on STI associated antibiotic use in the present. This means the slippage of antibiotics from 'solution' to 'non-solution' and even (in certain instances) to 'problem maker' (by increasing resistance) remains obfuscated.

Alongside syndromic care, STI care practices—which enable prevailing treatment cultures—subject bodies to routine surveillance, identifying disease and preparing bodies for microbial elimination. This in and of itself is not inherently positive or negative, but as noted by participants, needs to be thought about carefully in the context of resistant STIs. For instance, in Australia, pre-exposure prophylaxis (PrEP) to prevent HIV transmission was introduced in 2018, and guidelines suggest users of PrEP, predominantly men who have sex with men (MSM), are reviewed and tested every three months for HIV, syphilis, chlamydia and gonorrhoea (ASHM National Prep Guidelines, 2021). This has led to higher rates of testing within this group, as accessing PrEP requires a new script every 3 months, which includes the aforementioned screening. However, interviewees expressed concerns that these guidelines, and subsequent treatment cultures in the STI milieu, have led to over testing and subsequently even greater antibiotic use (Williams et al., 2023). This, interviewees stressed, is contributing to selective pressure on microbes to encourage resistance, yet is not reducing the prevalence of disease:

[A] lot of these patients that we pick up on asymptomatic screening, yes, okay, we might treat that asymptomatic rectal gonorrhoea in that patient and it might be gone for seven days or something, but then they might go right back into that same-sexual network where they haven't had all of those contacts treated and they might get it again a week later, two weeks later. There is evidence that a lot of these infections, asymptomatic infections, the body will clear by itself over a matter of weeks to months. So we're just peppering around these antibiotics, but I don't think we're making a difference.

(Clinician, Australia)

It's very hard to find any data anywhere in the world that says that test and treat actually reduces the prevalence [of microbes] in a population. You may reduce the harms of the organism, that's fair enough, but you don't reduce the prevalence. [...] So, I'm starting to change my mind on this and thinking that we should be perhaps more thinking of these organisms as commensals [able to be lived with] and not testing and not treating, because treating gonorrhoea in particular is just going to lead to more resistance because we're not going to do it perfectly. Antimicrobial resistance, antibiotic resistance has risen, prevalence is staying the same, so how are we winning in that sphere?

(Clinician, Australia)

As such, the introduction of new medications, like PrEP, becomes embedded within pre-existing logics and priorities that favour disease elimination as always good 'care', perpetuating and strengthening norms around this approach despite the downsides:

And I think part of that is that, as healthcare providers, the contract is between you and that patient that's in front of you, that you want to do the best for, not the next patient, the patient after, or the patient in two weeks, or the patient who's out in the community who will be potentially affected by how you deliver antibiotics today. So, there's this disconnect between the practise of medicine and that surrounding issue of AMR.

(Expert, Europe)

Such care practices, seeking to eliminate disease, were also evident in presumptive antibiotic use (although a decreasing measure now), where contacts of a known STI case are treated on the assumption they may have the disease. In these circumstances antibiotic use is premised on an imagined future, where an infected subject carries a disease, and such an imagining is then embroiled within a logic of disease elimination even if the disease itself does not necessarily exist. As a participant explained:

... I think we were always of the view, in my earlier days, probably the first 20 years, 25 years of my career, that if someone was a named contact they would be treated. And I think a lot of the nurses, especially the older nurses still feel that way because that's what's been drummed into us. If you're a contact, you get treated. But there's been more and more studies [...] that suggests that you don't need to do that for most people, and that it may well be a better use of resources not to treat that individual at that particular time, but to wait until we get a result [...] but certainly clinician sentiment has changed in that I think we can see that evolving to wait until we get a result back.

(Clinician, Australia)

As suggested, the use of PrEP itself is also underpinned by an imagined future, where one may contract HIV, and therefore the body is '(pre)treated' to prevent this from happening. Interviews reveal that such future thinking within treatment cultures, and the epitomisation of the disease-free body as 'health', creates an immediacy in the treatment of STIs such as gonorrhoea and chlamydia. As stated, such short-term thinking does little to consider the future of the antibiotic itself, or, more importantly, to account for a future where resistance may become

the norm for STIs. Moreover, instances of syndromic and presumptive antibiotic 'treatment' can be conceptualised part of broader 'covering' practices, where antibiotics are used for fear of adverse impacts if they are not administered (see Dixon et al., 2021), and can therefore also be seen as care.

Remarkably, and somewhat paradoxically, at present, unlike other STIs, *Mycoplasma genitalium* is *not* part of standardised screening processes. One participant suggests an expedient reason for the disparity:

It's quite interesting, we do not screen for *Mycoplasma genitalium* in asymptomatic people. And the rate of carriage, about 10% in women and 6% with men. So we're very comfortable not screening that infection, and we're very comfortable not screening that in heterosexuals, but for some reason, chlamydia and gonorrhoea never fell into that group. And I think it's because *Mycoplasma genitalium* is very difficult to treat. So, I think that's why there's been a difference.

(Clinician, Australia)

Like other cultures, treatment cultures are also uneven and contradictory. In this instance, the treatment culture is 'at peace' with bodies occupying an unknown and liminal space of potentially being 'infected' and not in complete 'health'. The same approach, however, is not extended to gonorrhoea or chlamydia, suggesting cultural practices and imaginaries have historically congealed differently around particular infections and diseases, including the later discovery and research on *Mycoplasma genitalium* (Unemo & Jensen, 2017). However, importantly, the 'reification' of such practices exists alongside critique and an emergent counter-culture, which challenges normative ways of thinking about and doing treatment.

## Prefigurate cultures: Collateral damage and the logic of (microbial) protection

As outlined by our interviewees, the rise of AMR has begun to challenge existing treatment cultures in sexual health and STI intervention specifically, and prefigure alternative treatment cultures. Our interviews provided clear accounts of an emergent 'counter-culture' in STI care, driven by the notion that traditional STI care and antimicrobial use is short-sighted in an era of AMR. Clinicians spoke to the concerted efforts being made, in a practice setting, to reduce antibiotic use and shift treatment cultures, even if this meant pushing up against national guidelines and existing policy structures:

So we, for some time at [our clinic], and we sort of do our own thing a little bit, we don't necessarily follow the national guidelines, so we stopped presumptive antibiotic use in STD contacts some time ago. And I looked at it, the proportion infected previously, and then I relooked at [our data] last year, and it was actually only 30% were infected in that sample of 800. So it wasn't huge. That meant we didn't treat 70% of the contacts. We treated 30% and we gave them the right antibiotic for the right infection.

(Clinician, Australia)

Also going against cultural treatment assumptions of disengaged and 'immoral' actors, certain patients were also narrated as being highly reflexive about their antimicrobial

consumption, particularly as they engaged with (proliferating) health information in the public sphere. A growing number of patients, we heard, were thought to be increasingly concerned about their gut microbiome and how it might be affected by antibiotics. This was particularly the case among highly educated patients in urban centres:

And I talk to the gay and bisexual men who come in, and they actually don't like all the antibiotics they're getting, they are worried about their gut microbiome, they are worried about resistance. And it's just that we haven't actually engaged them in conversations to talk about, "How do we decrease screening? How would that go with you if we actually reduce screening? Would you feel that you were being deserted or would you feel that this would be a good step, and how do we go about it?" Because what we're doing is actually doing, I think, more harm than good.

(Clinician, Australia)

Treatment cultures are thus already 'objects' of intervention: as sites where actors can apply critical reflexivity to the 'doing' of treatment, shifting normative practices and contributing to the emergence of a counter-treatment culture. These concerns about gut microbiome, wider health and antibiotic use vis-à-vis STI treatment, also challenge contemporary western biomedical epistemologies. Such epistemologies tend to conceptualise disease and ailments as singular 'events' in need of treatment, as opposed to existing along a holistic continuum of mind–bodies and how interventions can have unintended consequences. That is to say, the concerns about gut microbiome articulated by patients to interviewees entails a rethinking of the mind–body link, as constituted by a complex system, where treatment and disease have consequences for the entire organism. Furthermore, the emergence of a counter-treatment culture can also be seen as constituted by a process of 're-designation', where antibiotics' meanings are being re-cast:

And I think if everyone could actually sit down and say, "Look, antibiotics are actually precious. They've made a huge difference to health in the last 100 years, but we're blowing them, and we should actually be being careful with them so that they can last a lot longer." Because the antibiotic pipeline is pretty restricted. There doesn't seem to be much coming on board, and there certainly won't be the level of new drugs with the level of resistance that's going on.

(Clinician, Australia)

As suggested earlier, this *reimagining* of antibiotics is about seeing them not only in the present, but also through a lens of futurity. In this way, contemporary meaning and practice around antibiotics comes to be shaped by imaginings of possible futures in which antibiotics are ineffective. The emergence of counter-cultural practices points to the way treatment cultures are always emergent from the contexts in which they are located, and speaks to the agency of social actors to shape them.

## Complexity of institutions

During interviews, participants also emphasised the importance of understanding how treatment cultures are shaped by the institutional contexts where treatment takes place. A treatment

culture, as it were, was very often highly dependent on institutional variations in what (and who) is available. That is, care is materialised through material resources, expertise, staffing, presence of allied health and so on. What you 'get' was talked about as shaped by the institutional environments at play, with participants specifically contrasting general practice with specialist sexual health clinics:

Just, for example, moxifloxacin, so once somebody has a result of macrolide-resistant *Mycoplasma genitalium*, the next drug of choice is moxifloxacin. And so many times at the [sexual health specific centre] we'll get either calls from GPs saying, "Look, I'm just sending this patient to you because I've prescribed them moxifloxacin and they can't afford it," or it's not available. Well, they won't really say it's available here. They'll send it to us because moxi is what is advised and moxi is free at the [sexual health specific centre]. [...] But if moxifloxacin was on the PBS and was as cheap as doxycycline, then that would make it very much easier for GPs to not faff around with azithromycin for macrolide-resistant MG.

(Clinician, Australia)

It was a common and critical finding across the interviews that treatment cultures are emergent through institutional forms (an elaborate tussle between the individual and contexts). Inappropriate testing, time pressure and unaffordability at general practices were talked about by participants as contributing to problematic treatment cultures. In Australia, 'affordability' as a 'personal barrier' to accessing moxifloxacin, for instance, did not exist in some (specialist sexual health) settings because it was available for free. While these observations may seem common sense, as articulated by our participants, they demonstrate how 'pressure points' are socially produced within the environments in which they emerge.

What was equally clear, however, is that institutions should not be conceptualised as siloes, as they can in fact inform one another. The treatment culture of a sexual health clinic can shape practices in a non-sexual health clinic, and vice-versa in a process of 'cultural enrichment', as one clinician explained:

And that's where a place like the [sexual health specific centre] is very good, because basically they're approachable, we can ring a sexual health physician or some clinician that has very good experience and they can supplement our information we get from guidelines.

(Clinician, Australia)

Expertise can flow and spill across spaces as sexual health clinics become 'resource nodes' within a broader network of clinics, providing important 'sub-cultural' knowledge and imparting transformative capacities to the treatment cultures of other clinics. Our data also demonstrated that the complexity surrounding treatment cultures exists alongside the complexity of people who enter these spaces, which shapes the way treatment is done.

## Complexity of people

An interviewee's reflections on patient engagement illustrates how treatment cultures emerge and evolve at the nexus of macrostructural forces, institutions and intersect with the

complexities of people's lived experiences. As such, treatment of STIs, like other forms of care, is 'historical', in that it is entwined with everyday practices of living, thinking and being (Mol, 2008). Following, what treatment means and feels like, will differ based on the person. Participants explained patients may wish to be treated more promptly due to stigma attached to homosexuality, a desire to return to their sexual lives and the 'ick factor' of having an STI (see also Broom et al., 2023):

I've seen a number of gay men who aren't out in their community, so they're actually super high risk for HIV and syphilis and all these things, but their GP doesn't know, they're not going to tell anyone, they are going to travel three hours to Melbourne to do all of that [medical] stuff. And the other thing is, it's not just the GP, it's also, well, who's working in the lab in that regional town? If you get that antibiotic, there's only very few indications for an injection of benzylpenicillin or for an IM injection of ceftriaxone. So then, does the pharmacy know? Does the receptionist know? It extends quite far as not just the GP. It's like, "Where do I take that prescription? Where do I get that blood test?" et cetera, et cetera.

(Clinician, Australia)

Echoing existent AMR research (Davis et al., 2020), clinicians also emphasised the value of seeing patients as co-collaborators, capable of meaningful involvement in their own care practices, and talked about how to work with them more productively:

And I think that I now do not routinely hand out scripts to all patients who come in with symptoms. I will either make a decision with them that we'll wait to see what they've got, or I will give them a script and say, "It really would be best not to fill it until you get a call from us, because it might not be the right antibiotic for you. If you get really—increase in your symptoms in the next 24, 48 hours, do start it. But if you don't, then let's just wait to see what you've got." And people are great about it. They're like, "Yeah, actually I don't really want to take antibiotics anyway." [...] So, I think it's dissemination of information in a really accessible way, and partnering with consumers so that they understand that their behaviour actually impacts on this problem and can be part of the solution to the problem, or can be part of accelerating the problem.

(Clinician, Australia)

Interviewees noted that in a multicultural country like Australia, with large numbers of new immigrants, community engagement would also need to account for the different treatment cultures that people are used to:

... I would be putting my money [...] in consumer education [...] So, consumer campaigns that really were co-designed with different populations. CALD [culturally and linguistically diverse] population, again, may come from countries where there's a lot of antibiotics swishing around, so I think that would be a really important community to have champions and co-designed campaigns for, as well as for doctors and nurses who are serving those communities as well. So, if I think about in terms of equity deserving groups in terms of this space, I do think that the

CALD groups would benefit a lot just around that health literacy, but it would need to be coming from them.

(Clinician, Australia)

This is not to suggest that immigrants only have 'needs', as all communities, dominant or minority, have 'culture' and 'contexts' that must be worked with (Chandra, 2021). Rather, interviewees highlighted the importance of '*meeting communities where they're at*' [Industry, US], to co-create viable and appropriate solutions, attuned to the complexities of subjectivities, and their relationship to treatment cultures (Hinchliffe, 2022).

## DISCUSSION

This study builds on the broader sociological scholarship of AMR (Brown & Nettleton, 2017b; Frid-Nielsen et al., 2019), which seeks to understand resistance relationally and culturally (e.g. Brown & Nettleton, 2017a; Davis et al., 2020)—as structurally embedded (e.g. Chandler, 2020; Dixon, et al., 2021; Tompson & Chandler, 2021)—and to explore the evolving tussles between immediate and future orientations (e.g. Will, 2018). This includes the complexities of how institutions, practices, patient subjectivities and professional norms assemble antibiotic use and resistance (Dixon et al., 2021; Rynkiewich et al., 2023; Tompson & Chandler, 2021) and work against change. Given most participants in this study have experience working in the Global North, our analysis of these processes is contextually limited, most specifically to Australia.

In light of the existent AMR scholarship, our study illustrates how stigma and taboo lead to processes of de-prioritisation, which has implications for the development of innovations, and subsequently the types of care (or not) that clinicians are able to provide, which may assist in curbing the rise of AMR. It also shows how resistance induces new tensions within the STI field pertaining to syndromic treatment and care, including the way patient subjectivities and contexts, such as homophobia or physical pain, may necessitate syndromic treatment, highlighting the challenge of balancing presents and futures in such a context. As such, the particularities of our case study extends sociological scholarship on AMR, by further complicating the ways in which resistance plays out across economic, institutional and clinical spheres. This inserts an important new layer to our comprehension of the bio-social dimensions of resistance, which is critical to both comprehension of AMR as a highly diversified scene, and important for gaining traction in any proposed solutions. In saying this, we note an analysis of treatment cultures may be limited in its generalisability. However, the concept nonetheless provides an abstraction for analytic enquiry, which helps to critically evaluate taken-for-granted ways of practising care and how it is produced, as we have done so in this study.

Importantly, present treatment cultures surrounding STIs are predominantly influenced by an ideology that a healthy body is pathogen free, relying on black and white definitions of what constitutes a 'pathogen' in the first place (Kenyon et al., 2022). In essence, as our participant's note, the consequence of this is subjecting bodies to regular surveillance and antimicrobial intervention: detecting, targeting and eliminating pathogens, as in the case of quarterly bacterial STI testing for PrEP users. This constructs 'sexual health' as being almost exclusively about individuals in the here and now, and relatively swift recoveries, that is, valorises immediacy. In the context of AMR, this black and white sensibility — which our participants often challenged — does little to consider collective health, holistic health or sustainable futures. By way of example, disrupting treatment cultures to allow a body to be 'unhealthy' or 'diseased' in the

present (e.g., by letting asymptomatic gonorrhoea remain untreated in cis men who exclusively have sex with other cis men (Wardley et al., 2023)) may ironically create the potential for healthier bodies in the future by contributing to broader efforts to curb AMR. Such a frame of reference shifts the emphasis away from the infection as a singular organism that causes disease in the present, to a more complex and panoramic understanding that considers the future of antibiotic use (see Kenyon et al., 2022 for an in-depth discussion). This exists in tension with positive aspects of treatment cultures as described by participants, where clinicians seek to provide genuine care, whilst considering the subjectivities and contexts of their patients.

As a result, a paradoxical relationship to treatment practices emerges at the crossroads of individual needs vis-à-vis broader concerns about the rise of resistant STIs. While participants understood the need to administer antibiotics in a more considered manner to preserve their efficacy, they simultaneously recognised that patients experiencing significant pain and discomfort should be treated, even if this is based on symptoms. As Mol (2008: 74) states, ‘in the logic of care attentiveness and specificity are good and neglect is bad’. The point is not to simply withhold treatment. Rather it is to take measures, where possible, such as reduced testing to not detect asymptomatic infections, or waiting for results to deliver more precise treatment, which may help curb the rise of AMR. Considering this, we argue that clinicians are balancing two forms of care, which includes care for the individual in the present, and care for the collective future that needs antibiotics to last. In this sense, clinicians must navigate the tensions of individualist and ecological frames, as they decide who to care for, and how, occupying positions at the intersection of the dominant treatment culture, concerns about AMR, and caring for their patients. While absent from this study, patient attitudes to STIs in the context of AMR will provide a deeper understanding of the relational dynamics of such care, and what they mean for resistance.

To some extent, clinician insights are already being integrated into treatment cultures, in everyday clinical practice. Cultures, after all, are changeable; not static. This means current over reliance on antibiotics in STI care can be ‘designed out’ (Dixon et al., 2021), to a degree, through cultural transformation. This was apparent in participant reflections concerning the counter-culture moves they are instigating. Thinking with the idea of a counter-culture shows how treatment cultures are already an object of enquiry open to reflexivity and critical evaluation, giving rise to new practices. These prefigurative actions also include reflections from patients themselves, who express concerns about their gut microbiome vis-à-vis routine antibiotic use, and therefore may be open to new care practices (Davis et al., 2020). However, as suggested throughout our analysis, the transformation of treatment cultures will also require policies that address structural issues (Kirchhelle et al., 2020), such as government-industrial relations vis-à-vis innovation, and the prioritisation of STIs in the first place. This includes centring traditionally ‘undeserving’ subjects, such as MSM and sex workers, within global AMR policies, where issues of stigma and prejudice can mean the neglect of these groups.

## CONCLUSION

This article demonstrates that a sociological framing of rising antibiotic resistance in STIs necessitates thinking about treatment as a cultural production to further develop a panoramic and relational understanding of the transformations that can curb resistance. Data illustrate that treatment cultures are assembled through the interaction of political priorities, economic considerations, taken-for-granted clinical practices and an orientation towards the present. However, these normative practices are also subject to intervention, where clinicians critically

evaluate treatment, which gives rise to counter-cultural practices. This bottom-up approach involves re-designating antibiotics as precious resources, which need to be used carefully with an orientation towards the future. Ultimately, findings demonstrate that a relational and networked solution is required, where governments better support industry for scientific innovation, and share in cost-benefits. This has potential flow-on effects to increase efficiency of testing and treatment, and the subsequent transformation of clinical practice, alongside a critical rethinking of the meaning of care, infection elimination and a future-orientated approach to antibiotics, involving tailored engagements with community members. As such, future research should consider exploring community understandings of AMR and STIs, their relation to people's sexual practices and reflections on potential solutions to the curb the rise of resistance (e.g. reduction of testing for MSM). This will be crucial for developing interventions that speak to people's everyday realities and experiences of sexual pleasure. Moreover, to develop appropriate relational and networked solutions, further research should also focus on other localised contexts, including different regions within the Global North. This will provide valuable insight into existent local sexual health infrastructures, and constructions of sexuality, as they relate to the nuances of addressing antibiotic resistant STIs globally.

## AUTHOR CONTRIBUTIONS

**Shiva Chandra:** Conceptualization (lead); formal analysis (equal); writing—original draft (equal); writing—review & editing (equal). **Alex Broom:** Conceptualization (lead); formal analysis (equal); funding acquisition (lead); methodology (equal); writing—original draft (equal); investigation (supporting); writing—review & editing (equal). **Damien Ridge:** Writing—review & editing (supporting). **Michelle Peterie:** Formal analysis (equal); investigation (lead); methodology (equal); project administration (lead); writing—review & editing (supporting). **Lise Lafferty:** Investigation (supporting); writing—review & editing (supporting). **Jennifer Broom:** Writing—review & editing (supporting). **Katherine Kenny:** Writing—review & editing (supporting). **Carla Treloar:** Writing—review & editing (supporting). **Tanya Applegate:** Writing—review & editing (supporting).

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## CONFLICT OF INTEREST STATEMENT

There are no conflicts of interests to declare.

## DATA AVAILABILITY STATEMENT

Due to the nature of the study and to protect participant confidentiality, the data from this study are not publicly available.

## ETHICS STATEMENT

Ethics approval was sought and granted from University of Sydney's Human Research Ethics Committee (reference: 2022/128).

## PATIENT CONSENT STATEMENT

N/A.

**PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES**

N/A.

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<sup>1</sup> This article draws on a broad definition of culture as a way of life and by extension approaches to STIs similarly constitute a way of doing treatment (see Jenks, 2005 for an in-depth discussion of definitions of culture).

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# HIV Infection in Adults: Initial Management

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The HIV epidemic is an important public health priority. Transmissions continue to occur despite effective therapies that make HIV preventable and treatable. Approximately one-half of people with HIV are not receiving suppressive antiretroviral therapy (ART). Starting ART early, followed by continuous lifetime treatment, most effectively achieves durable virologic suppression and restoration of immune function that can improve clinical outcomes and prevent transmission to partners who are seronegative. National treatment guidelines include ART options that can be offered immediately after diagnosis, even before the results of baseline HIV drug-resistance testing are available. Initial ART selection should be guided by co-occurring conditions, including viral hepatitis, medications, and other factors such as pregnancy. Identifying and addressing psychosocial barriers to care is a key element of ensuring long-term adherence to treatment. The initial physical examination typically reveals no clinical manifestations of HIV in the absence of advanced disease. A comprehensive laboratory evaluation, including HIV viral load and CD4 lymphocyte monitoring, is necessary to guide decision-making for treatment, opportunistic infection prophylaxis, and vaccinations. The initial management of people with HIV presents a unique opportunity for family physicians to improve patients' long-term health care and reduce HIV transmissions. (*Am Fam Physician*. 2021;103(7):407-416. Copyright © 2021 American Academy of Family Physicians.)



**One-half of the** estimated 1.1 million people in the United States with HIV infection are not receiving antiretroviral therapy (ART) or are receiving ART that is not sufficiently effective to achieve key clinical outcomes. Key outcomes include preventing clinical progression to advanced HIV disease, allowing near-normal life expectancy, and reducing transmission risk (i.e., treatment as prevention).<sup>1-8</sup> HIV disproportionately affects people of color and people with limited access to continuous, comprehensive health care.<sup>9,10</sup> Family physicians are uniquely positioned to diagnose HIV early and ensure long-term quality care for patients.

## Diagnosis

HIV screening and diagnostic testing are essential for timely ART initiation and transmission prevention because approximately 38% of new transmissions are from people

with HIV who are unaware of their HIV status.<sup>2</sup> Testing with the fourth-generation combination HIV antigen-antibody immunoassay is widely available and is recommended for screening people 15 to 65 years of age and for testing people with risk factors<sup>11-14</sup> (Table 1). In addition to HIV-specific immunoglobulin M and immunoglobulin G antibodies,

## WHAT'S NEW ON THIS TOPIC

### HIV Infection in Adults

Nearly one-half of the estimated 1.1 million people with HIV infection in the United States are not receiving antiretroviral therapy or are receiving antiretroviral therapy that is not sufficiently effective to achieve the key clinical outcomes.

Approximately 38% of new transmissions are from people with HIV who do not know their HIV status.

Clinicians should identify and address potential barriers to treatment and adherence, including concerns for unintended disclosure of HIV status, housing and food instability, transportation challenges or conflicting priorities, and lack of patient readiness or motivation.

**CME** This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 401.

**Author disclosure:** No relevant financial affiliations.

**Patient information:** A handout on this topic is available at <https://familydoctor.org/condition/hiv>.

Illustration by Dave Klemm

## BEST PRACTICES IN INFECTIOUS DISEASE

## Recommendations from the Choosing Wisely Campaign

Recommendation	Sponsoring organization
Do not routinely test for cytomegalovirus immuno-globulin G in patients with HIV infection who have a high likelihood of being infected with cytomegalovirus.	HIV Medicine Association

**Source:** For more information on the Choosing Wisely Campaign, see <https://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <https://www.aafp.org/afp/recommendations/search.htm>.

which typically develop three or more weeks following infection, the fourth-generation HIV test detects the p24 antigen that appears as early as two weeks after infection. Inclusion of the p24 antigen shortens the time frame for detecting HIV, increasing the likelihood of identifying people with HIV who recently acquired the infection (i.e., within the previous one to two months).

The risk of HIV transmission from untreated people with acute or early HIV infection is much higher than from people with established chronic infection who are receiving suppressive ART. Therefore, improved identification of acute infection allows for earlier intervention, including ART initiation and education about transmission prevention (i.e., pre- and postexposure prophylaxis for partners who are seronegative).<sup>15–18</sup> Acute symptomatic HIV is often unrecognized, and fewer than 50% of people will have an identifiable acute illness.<sup>19</sup> Many respiratory illnesses, including those caused by SARS-CoV-2 or influenza, are more common; therefore, a careful assessment of recent risk behaviors and exposures may be a factor that prompts HIV testing.

**Evaluation****HISTORY AND PHYSICAL EXAMINATION**

After a diagnosis of HIV, the initial history should document details about other chronic health conditions, hospitalizations, medications and allergies, mental and behavioral health, substance use, sexual health history, and experience with HIV pre- or postexposure prophylaxis. For people with advanced HIV, which is generally indicated by a CD4 lymphocyte count of less than 200 cells per  $\mu\text{L}$  ( $0.20 \times 10^9$  per L), a full review of systems to assess for opportunistic infections or conditions associated with significant immunosuppression such as *Pneumocystis jirovecii* pneumonia, oropharyngeal candidiasis, tuberculosis, HIV-associated central nervous system and

gastrointestinal disorders, and disseminated fungal or viral infections is recommended. When patients with chronic HIV infection reengage in care, clinicians should obtain a comprehensive history of previous ART regimens and treatment responses, including previous laboratory results. The initial examination generally shows no specific HIV-related manifestations unless symptomatic acute infection or advanced HIV disease is present.

**LABORATORY TESTING**

The diagnosis of HIV should be established with documented laboratory test results. Abnormal results from home-based, point-of-care, or rapid tests should be followed with standard, instrument-based laboratory assays. After the diagnosis is confirmed, comprehensive testing should be ordered (Table 2).<sup>4,20</sup> Testing should include primary care screening and HIV-specific baseline laboratory testing with a CD4 count, quantitative plasma HIV RNA (viral load), and HIV drug-resistance assessment. The CD4 count reflects the degree of immune system impairment and helps determine if opportunistic infection prophylaxis is indicated. The HIV viral load indicates how much active viral replication is occurring. Regular viral load monitoring during treatment is the most important indicator

**TABLE 1****HIV Screening and Testing in Primary Care**

Screen all people 15 to 65 years of age at least once; younger adolescents and older adults at increased risk should also be screened.\* Retest people who are at increased risk of infection.

Screen all pregnant people, including those who present in labor or at delivery whose HIV status is unknown.

Screen all patients being considered for pre- and postexposure prophylaxis according to established guidelines.

Test when acute HIV infection is suspected in people with recent exposure history (i.e., within the previous two months) and symptoms of recent viral infection, including fever, chills, night sweats, fatigue, myalgia, lymphadenopathy, headache, sore throat, and diarrhea.

Test when chronic HIV infection is suspected, based on clinical presentation and risk or exposure history. Symptoms of chronic untreated HIV include fever, lymphadenopathy, malaise or fatigue, weight loss, and symptoms from undiagnosed opportunistic infections.

\*—Recommendation of U.S. Preventive Services Task Force, endorsed by the American Academy of Family Physicians. Note that the Centers for Disease Control and Prevention recommends screening for people 13 to 64 years of age.

## HIV INFECTION

**TABLE 2**

### Recommended Baseline and Follow-up Laboratory Testing After HIV Diagnosis

Baseline testing	Follow-up testing interval and comments
<b>HIV-specific tests</b>	
CD4 lymphocyte count	Three months after ART initiation, then every three to six months until two years; can decrease to every 12 months if CD4 count is $> 300$ cells per $\mu\text{L}$ ( $0.30 \times 10^9$ per L) for two years with consistently suppressed viral load; CD4 monitoring is optional if CD4 count is consistently $> 500$ cells per $\mu\text{L}$ ( $0.50 \times 10^9$ per L) for two years with a consistently suppressed viral load
HIV drug resistance (i.e., genotype)	Consider repeat resistance testing for virologic failure (i.e., inability to achieve or maintain HIV RNA $< 200$ copies per mL)
HIV RNA (viral load)	Repeat within two to eight weeks after ART initiation; repeat every four to eight weeks until viral load is lower than the assay's lower limit of detection (undetectable); for patients on stable, suppressive ART, repeat every three to four months until two years, and thereafter every six months if clinically, immunologically, and virologically stable
<b>Other HIV-related tests</b>	
HLA-B*5701 only if considering abacavir (Ziagen)-containing regimens	To avoid serious hypersensitivity reactions
Hepatitis A, B, and C serologies	Following at-risk exposures or based on clinical presentation
Sexually transmitted infections (e.g., chlamydia, gonorrhea, syphilis, trichomoniasis)	Following at-risk exposures or based on clinical presentation
Tuberculosis (tuberculin skin test or interferon-gamma release assay)	Annually, based on risk; tuberculin skin test result of 5 mm is positive in people with HIV; chest radiography recommended for a positive result or if the patient has a history of tuberculosis; patients with advanced HIV disease can have false-negative results; repeat screening after ART-restored immunocompetence
<b>Standard tests</b>	
Chemistry profile, including hepatic and renal function tests, protein, and albumin	Two to eight weeks, then three to six months; serum phosphorus should be monitored in patients with chronic kidney disease who are taking tenofovir disoproxil fumarate (Viread)-containing regimens
Complete blood count with differential	Three to six months; then every 12 months when no longer monitoring CD4 counts
Fasting blood glucose or A1C	Three to six months, then at least annually
Fasting or random serum lipids	Annually
HPV-related anogenital cancer screening	Cervical cytology: six to 12 months, then every three years if the initial three results were normal; abnormal results require additional evaluation (i.e., reflex human papillomavirus testing, colposcopy); human papillomavirus cotesting is not recommended in women $< 30$ years; in women $\geq 30$ years, follow-up screening should be performed every three years if human papillomavirus and Papanicolaou test results are normal
Pregnancy test	No national recommendations exist for routine anal cancer screening; some experts recommend anal cytologic screening and high-resolution anoscopy for men and women who are HIV seropositive; others recommend screening in high-risk subgroups only (e.g., anogenital condylomata, men who have sex with men); anal cytology screening should not be performed without the availability of referral for high-resolution anoscopy
Urinalysis	When indicated

ART = antiretroviral therapy.

Information from references 4 and 20.

of a response to ART. HIV drug-resistance testing guides the initial selection of the ART regimen by identifying clinically significant mutations in the genes (reverse transcriptase, protease, integrase) targeted by commonly used antiretroviral drugs. Commercially available resistance tests are generally highly sensitive and accurate. Studies have established the clinical and cost-effectiveness of baseline resistance testing.<sup>21</sup>

## Initial Management

### ANTIRETROVIRAL THERAPY

ART should be started as soon as possible after diagnosis to reduce HIV-related morbidity and mortality and reduce transmission risk.<sup>4,20</sup> Durable suppression of viremia facilitates immunologic recovery and may mitigate HIV-associated inflammation and immune activation that contributes to end-organ damage. Physicians should regularly emphasize the importance of medication adherence because suboptimal ART adherence can promote HIV drug resistance and complicate or limit future treatment options.

Patients and clinicians should attempt to identify and address potential barriers to treatment and adherence, including concerns for unintended disclosure of HIV status, housing and food instability, difficulties in attending appointments because of transportation challenges or conflicting priorities, and lack of patient readiness and motivation. Psychiatric disorders, substance use, and psychosocial challenges should not be reasons to withhold ART. Patient-centered strategies to support adherence and engagement in care are pivotal to achieving desired health outcomes. It is essential to establish how medical services and treatment costs will be covered. In addition to insurance with or without copays, HIV-specific programs such as the Ryan White HIV/AIDS Treatment Extension Act of 2009 Part B and AIDS Drug Assistance Programs can lower the cost barrier for patients. Social services, case management, HIV education and counseling, and additional support services are often critical for a successful care plan.

ART can be initiated before baseline drug-resistance test results are obtained for patients who are pregnant, patients with acute or recent HIV infection, and when the patient and physician decide to start ART immediately after diagnosis. Benefits of ART initiation immediately or soon after diagnosis include increased patient engagement in care, faster time to virologic suppression, and decreased transmission risk.<sup>22</sup> Once drug-resistance testing results are available, treatment can be adjusted if indicated.

Immediate ART initiation may not be advisable if a serious untreated opportunistic infection is present, specifically

one involving the central nervous system.<sup>4,20</sup> In such cases, opportunistic infection treatment should begin before ART to decrease the risk of immune reconstitution inflammatory syndrome, which is an exaggerated inflammatory reaction resulting from activation of latent infections, malignancies, or other conditions that occur with ART-induced immune system recovery. Expert guidance is recommended.<sup>4,23</sup> Patients who are not ready to start ART immediately after diagnosis should be followed closely and supported, with frequent reevaluation of medication readiness and barriers to initiating treatment.

Initial ART selection for patients who have not received treatment previously is guided by patient preference, baseline laboratory results (including hepatic and renal function tests), adverse effect and drug interaction profiles, viral hepatitis coinfection and other comorbidities, and drug allergies (Table 3<sup>4,20</sup>). Once-daily and single-tablet regimens are widely available and covered by many HIV/AIDS drug assistance programs.

ART response is monitored by sequential measurement of viral load and CD4 counts. Optimal virologic suppression is a confirmed HIV RNA level persistently below the lower limit of detection (undetectable), which varies by assay. Undetectable levels are typically achieved in eight to 24 weeks, depending on pretreatment viral load and ART selected. Failure to achieve sustained virologic suppression by 24 weeks should prompt an assessment of adherence and ART drug absorption or interactions. CD4 count is less helpful for assessing initial response to ART because changes in CD4 count predictably follow changes in viral load. Table 2 provides recommended intervals for laboratory monitoring.<sup>4,20</sup> Patients with low CD4 counts starting or resuming ART should be monitored closely for immune reconstitution inflammatory syndrome during the first weeks to months after treatment initiation.<sup>4,20</sup>

### OPPORTUNISTIC INFECTIONS

Primary chemoprophylaxis against *P. jiroveci* pneumonia is recommended for people with CD4 counts less than 200 cells per  $\mu\text{L}$  and can be discontinued when CD4 counts increase with treatment to greater than 200 cells per  $\mu\text{L}$  for at least three months.<sup>23</sup> Patients with CD4 counts less than 100 cells per  $\mu\text{L}$  ( $0.10 \times 10^9$  per L) who are *Toxoplasma* seropositive require chemoprophylaxis against *Toxoplasma gondii*<sup>23</sup>; trimethoprim/sulfamethoxazole or atovaquone (Mepron) offers sufficient prophylaxis against both. Primary prophylaxis against disseminated *Mycobacterium avium* is unnecessary for people with HIV who immediately initiate ART, but it is recommended for people who have HIV with CD4 counts less than 50 cells per  $\mu\text{L}$  ( $0.05 \times 10^9$  per L) who are not receiving ART.

## HIV INFECTION

**TABLE 3**

### Recommended Initial Antiretroviral Regimens for Most Treatment-Naive Adults with HIV\*

Regimen	Adverse effects and comments†
Bictegravir, 50 mg/ emtricitabine, 200 mg/ tenofovir alafenamide, 25 mg (Biktarvy), once daily	Bictegravir/emtricitabine/tenofovir alafenamide is one of the preferred options if initiating antiretroviral therapy before baseline resistance testing results are available  Not recommended for patients with creatinine clearance < 30 mL per minute per 1.73 m <sup>2</sup>  Bictegravir inhibits secretion of creatinine and can lead to slight increase in serum creatinine levels without affecting actual renal function  Patients with hepatitis B virus coinfection may be at increased risk of hepatitis flare when this medication is discontinued  Refer to drug interaction resources for dosing instructions if taken with polyvalent cations (e.g., antacids, supplements)
Abacavir, 600 mg/dolute- gravir, 50 mg/lamivudine, 300 mg (Triumeq), once daily	Do not use abacavir if <i>HLA-B*5701</i> test is positive  Not recommended for patients with creatinine clearance < 50 mL per minute per 1.73 m <sup>2</sup>  Dolutegravir inhibits secretion of creatinine and can lead to slight increase in serum creatinine levels without affecting renal function  Patients with hepatitis B or C coinfection are at increased risk of transaminase elevation with dolutegravir use; risk of hepatitis flare in patients with hepatitis B when this medication is discontinued  Dolutegravir is relatively lipid- and glucose-neutral but has been linked to weight gain  Refer to drug interaction resources for dosing instructions when taken with polyvalent cations (e.g., antacids, supplements)
Dolutegravir, 50 mg (Tivicay), once daily  <i>Plus, any of the following:</i>  Emtricitabine, 200 mg/ tenofovir disoproxil fumarate, 300 mg (Tru- vada), once daily  or  Emtricitabine, 200 mg/ tenofovir alafenamide, 25 mg (Descovy), once daily  or  Lamivudine, 300 mg/ tenofovir disoproxil fumarate, 300 mg (Cim- duo), once daily	Dolutegravir-based regimens are among the preferred options if initiating antiretroviral therapy before baseline resistance testing results are available  Dolutegravir inhibits secretion of creatinine and can lead to a slight increase in serum creatinine levels without affecting renal function  Patients with hepatitis B or C virus coinfection may be at increased risk of transaminase elevation with dolutegravir use  Dolutegravir is relatively lipid- and glucose-neutral but it has been linked to weight gain  Refer to drug interaction resources for dosing instructions when taken with polyvalent cations (e.g., antacids, supplements)  Tenofovir disoproxil fumarate use increases risk of nephrotoxicity and decreased bone mineral density; consider alternative (e.g., tenofovir alafenamide) in patients with or at risk of renal disease or osteopenia/osteoporosis; use with caution in patients who are taking nephrotoxic agents  Risk of hepatitis flare in patients with hepatitis B when emtricitabine/tenofovir disoproxil fumarate is discontinued (similar caution if emtricitabine/tenofovir alafenamide or lamivudine/tenofovir disoproxil fumarate is discontinued)  Lower risk of renal dysfunction and bone mineral loss with tenofovir alafenamide than with tenofovir disoproxil fumarate, but possibly less favorable effects on lipid levels and weight gain  Avoid emtricitabine/tenofovir disoproxil fumarate if creatinine clearance < 60 mL per minute per 1.73 m <sup>2</sup> Emtricitabine/tenofovir alafenamide is not recommended in patients with creatinine clearance < 30 mL per minute per 1.73 m <sup>2</sup>  Lamivudine/tenofovir disoproxil fumarate is not recommended in patients with creatinine clearance < 50 mL per minute per 1.73 m <sup>2</sup>

*continues*

**Note:** The Department of Health and Human Services guidelines are updated frequently.<sup>4</sup> Recommendations are also available from the International Antiviral Society-USA.<sup>20</sup>

\*—Antiretroviral use in pregnancy should be guided by expert consultation and/or established treatment guidelines.

†—For a complete list of adverse effects, drug interactions, and contraindications, clinicians can consult the National Clinician Consultation Center at 800-933-3413, or access antiretroviral drug tables at <http://www.nccc.ucsf.edu>. Comprehensive antiretroviral information is available in the Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Information is also available at the National HIV Curriculum (<https://www.hiv.uw.edu>) and via the University of Liverpool's HIV Drug Interactions website (<https://www.hiv-druginteractions.org>) and Toronto General Hospital drug interaction tables (<https://hivclinic.ca/drug-information/drug-interaction-tables>).

## HIV INFECTION

**TABLE 3** (continued)

### Recommended Initial Antiretroviral Regimens for Most Treatment-Naive Adults with HIV\*

Regimen	Adverse effects and comments†
Dolutegravir, 50 mg/lamivudine, 300 mg (Dovato), once daily	<p>Do not use if initial HIV RNA &gt; 500,000 copies per mL, hepatitis B virus coinfection, or before a review of resistance testing and hepatitis B screening results</p> <p>May be preferred by patients who wish to take fewer medications (i.e., two-drug vs. three-drug regimens)</p> <p>Not recommended in patients with creatinine clearance &lt; 50 mL per minute per <math>1.73\text{ m}^2</math></p> <p>Dolutegravir inhibits secretion of creatinine and can lead to slight increase in serum creatinine levels without affecting renal function</p> <p>Patients with hepatitis B or C virus coinfection are at increased risk of transaminase elevation with dolutegravir use</p> <p>Dolutegravir is relatively lipid- and glucose-neutral but has been linked to weight gain</p> <p>Refer to drug interaction resources for dosing instructions when taken with polyvalent cations (e.g., antacids, supplements)</p>
Raltegravir, 400 mg (Isentress), twice daily	Raltegravir is relatively well tolerated and lipid- and glucose-neutral; has been associated with increased creatinine phosphokinase levels, myopathy, and rhabdomyolysis
<i>Plus, any of the following:</i>	<p>More experience in pregnancy compared with dolutegravir and bictegravir</p> <p>Tenofovir disoproxil fumarate use increases risk of nephrotoxicity and decreased bone mineral density; consider alternative (e.g., tenofovir alafenamide) in patients with or at risk of renal disease or osteopenia/osteoporosis; use with caution in patients who are taking nephrotoxic agents</p> <p>Risk of hepatitis flare in patients with hepatitis B when disoproxil fumarate is discontinued</p> <p>Lower risk of renal dysfunction and bone mineral loss with tenofovir alafenamide than tenofovir disoproxil fumarate, but possibly less favorable effects on lipid levels and weight gain</p> <p>Avoid emtricitabine/tenofovir disoproxil fumarate if creatinine clearance &lt; 60 mL per minute per <math>1.73\text{ m}^2</math></p> <p>Emtricitabine/tenofovir alafenamide is not recommended in patients with creatinine clearance &lt; 30 mL per minute per <math>1.73\text{ m}^2</math></p> <p>Lamivudine/tenofovir disoproxil fumarate is not recommended in patients with creatinine clearance &lt; 50 mL per minute per <math>1.73\text{ m}^2</math></p>
Emtricitabine, 200 mg/tenofovir disoproxil fumarate, 300 mg, once daily or Emtricitabine, 200 mg/tenofovir alafenamide, 25 mg, once daily or Lamivudine, 300 mg/tenofovir disoproxil fumarate, 300 mg, once daily	

**Note:** The Department of Health and Human Services guidelines are updated frequently.<sup>4</sup> Recommendations are also available from the International Antiviral Society-USA.<sup>20</sup>

\*—Antiretroviral use in pregnancy should be guided by expert consultation and/or established treatment guidelines.

†—For a complete list of adverse effects, drug interactions, and contraindications, clinicians can consult the National Clinician Consultation Center at 800-933-3413, or access antiretroviral drug tables at <http://www.nccc.ucsf.edu>. Comprehensive antiretroviral information is available in the Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Information is also available at the National HIV Curriculum (<https://www.hiv.uw.edu>) and via the University of Liverpool's HIV Drug Interactions website (<https://www.hiv-druginteractions.org>) and Toronto General Hospital drug interaction tables (<https://hivclinic.ca/drug-information/drug-interaction-tables>).

Information from references 4 and 20.

## IMMUNIZATIONS

Table 4 lists recommended immunizations for certain vaccine-preventable conditions (e.g., community-acquired pneumonia, hepatitis B).<sup>23,24</sup> Live vaccines should be avoided in people with CD4 counts less than 200 cells per  $\mu\text{L}$ . Additionally, people who have HIV with low CD4 counts may have suboptimal vaccination responses. Updated guidance on vaccination management for people who have HIV with low CD4 counts is available.<sup>24</sup>

## PSYCHOSOCIAL ASPECTS OF HIV PRIMARY CARE

Psychosocial factors can be central to developing therapeutic relationships with patients and identifying strategies to provide long-term, person-centered care. Psychosocial factors include consideration of the patient's social, family, and community support networks; housing, financial, and employment status; access to health insurance and medication coverage; concerns about stigma and unwanted disclosure; a history of trauma or interpersonal violence; and impact

of racial and gender bias on their health and health care.<sup>25-27</sup> Assessing how patients self-identify (he/she/they) and knowing whether and how to share that information with family members or associates can be extremely beneficial in developing a therapeutic relationship.

### IMPORTANT CO-OCCURRING CONDITIONS

Coinfection with hepatitis B or C should be treated per established guidelines, with attention to drug-drug interactions.<sup>28,29</sup> Some HIV antiretroviral drugs are also active against hepatitis B; if these medications are discontinued, a hepatitis B flare can occur with significant transaminase elevation. Standard hepatocellular carcinoma screening should be performed if indicated.<sup>30</sup>

Substance use can impact treatment adherence and engagement in care. Because substance use disproportionately affects people with HIV, all patients should be screened and treated for substance use disorders.

HIV infection itself, and some antiretroviral medications, can impair multiple organ systems and lead to renal and hepatic disease; cognitive, motor, sensory, and neurologic deficits; osteopenia or osteoporosis; metabolic complications including diabetes mellitus and dyslipidemia; and chronic cardiopulmonary disorders.<sup>25,31</sup>

### PREGNANT PEOPLE AND OLDER ADULTS

Perinatal HIV transmission is rare in the United States because of high rates of antenatal HIV screening and effective ART use through pregnancy and delivery. All pregnant people should be screened for HIV.<sup>12,14</sup> Pregnant people with HIV and people planning to conceive should maintain continuous, suppressive ART throughout pregnancy to reduce the risk of perinatal transmission.<sup>32</sup> Because the postpartum period has unique challenges, clinicians are encouraged to coordinate early with other clinicians and health care team

members (e.g., case managers, social workers, adherence counselors) to provide continuing care after delivery.<sup>33,34</sup> Perinatally-exposed infants are generally managed in conjunction with pediatric HIV or infectious disease specialists.

TABLE 4

### Immunizations for Adults with HIV

Vaccine	Indication
Hepatitis A	All susceptible people with HIV; single preparation (Twinrix) available if administering with a hepatitis B vaccine
Hepatitis B*	All susceptible people with HIV Not required if: hepatitis B surface antibody and core antibodies are both positive <i>or</i> Hepatitis B surface antibody is positive after a previous complete vaccine series See guidelines for serologic scenarios, immunization schedules, and preparations (e.g., two- or three-dose series)†
Herpes zoster	Recombinant zoster vaccine (Shingrix) recommended for people $\geq 50$ years
Human papillomavirus	Standard schedule; if not fully immunized, a catch-up immunization is indicated through 26 years of age; shared decision-making for 27 to 45 years of age
Influenza (inactivated only)	Standard schedule; high dose usually recommended; live attenuated influenza vaccine contraindicated
Meningococcal	All people with HIV
Pneumococcal	All people with HIV‡
Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap)	Standard schedule

**Note:** Adults with a CD4 count  $< 200$  cells per  $\mu\text{L}$  should not receive live vaccines. Refer to the Advisory Committee on Immunization Practices and the Department of Health and Human Services guidelines for considerations about vaccination for measles, mumps, and rubella and varicella-zoster virus for adults with HIV.

\*—The guidelines for hepatitis B and people with HIV are being updated. For the latest information, see <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/344/hepatitis-b-virus>.

†—Some experts recommend double-dose hepatitis B vaccinations, especially if the patient does not respond to the initial vaccination series.

‡—Adults who have never received a pneumococcal vaccine should receive a single dose of the 13-valent pneumococcal conjugate vaccine (regardless of CD4 count). People with a CD4 count of  $\geq 200$  cells per  $\mu\text{L}$  should then receive one dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least eight weeks later (can offer to people with a CD4 count  $< 200$  cells per  $\mu\text{L}$ ; however, PPSV23 should preferably be deferred until after the CD4 count increases to  $> 200$  cells per  $\mu\text{L}$  with antiretroviral therapy). Administer a single revaccination dose of PPSV23 at least five years after previous PPSV23 dose. Administer a final dose of PPSV23 after 65 years of age (and should be administered at least five years after any doses that were given before age 65).

Information from references 23 and 24.

## HIV INFECTION

### SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
All people 15 to 65 years of age should be screened for HIV at least once; all people who are pregnant should be screened for HIV. <sup>12</sup>	A	U.S. Preventive Services Task Force recommendations based on systematic review of high-quality patient-oriented evidence
Combination antiretroviral therapy should be initiated as soon as possible after HIV diagnosis. <sup>4,20</sup>	C	Department of Health and Human Services guidelines based on epidemiologic and modeling studies; consensus guidelines from the International Antiviral Society–USA Panel
Combination antiretroviral therapy with durable viral load suppression is recommended for people with HIV to reduce the risk of sexual transmission to seronegative partners. <sup>4–8,20</sup>	C	Department of Health and Human Services guidelines based on randomized controlled trials of serodiscordant couples; consensus guidelines from the International Antiviral Society–USA Panel
If the CD4 count is less than 200 cells per µL ( $0.20 \times 10^9$ per L), prophylaxis against <i>Pneumocystis jiroveci</i> should be initiated. <sup>23</sup>	C	Department of Health and Human Services guidelines based on retrospective studies
If the CD4 count is less than 100 cells per µL ( $0.10 \times 10^9$ per L) and <i>Toxoplasma</i> antibodies are positive, prophylaxis against <i>Toxoplasma gondii</i> should be initiated. <sup>23</sup>	C	Department of Health and Human Services guidelines based on retrospective studies
Most vaccinations can be administered according to standard adult vaccination schedules; live vaccines should be avoided in people with a CD4 count less than 200 cells per µL. <sup>23,24</sup>	C	Department of Health and Human Services guidelines based on expert opinion

**A** = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <https://www.aafp.org/afpsort>.

TABLE 5

### HIV Clinical Resources

Resource	Contact information	Comments
AIDS Education and Training Centers Program	<a href="https://aidsetc.org/">https://aidsetc.org/</a>	Webinars, courses, and training for preventing and treating HIV
HIV Info	<a href="https://aidsinfo.nih.gov">https://aidsinfo.nih.gov</a>	Department of Health and Human Services practice guidelines
International Antiviral Society–USA	<a href="https://www.iasusa.org">https://www.iasusa.org</a>	Webinars, courses
National Clinician Consultation Center, HIV/AIDS Management	<a href="https://nccc.ucsf.edu">https://nccc.ucsf.edu</a> 800-933-3413	Information and guidance for clinicians, available free from experts in HIV prevention, treatment, and HIV comorbidities including viral hepatitis and substance use; most calls are answered live and provide guidance at the point of care
National Clinician Consultation Center, Hepatitis C	844-437-4636	Managing HIV and hepatitis C coinfections
National Clinician Consultation Center, Perinatal HIV/AIDS Consultation	888-448-8765	Managing HIV in pregnancy, preventing perinatal transmission, caring for HIV-exposed infants
National HIV Curriculum	<a href="https://www.hiv.uw.edu">https://www.hiv.uw.edu</a>	Online modules and summaries of core HIV information
Postexposure Prophylaxis Hotline (PEPline)	888-448-4911	Managing occupational and nonoccupational exposures
Preexposure Prophylaxis Hotline (PrEPline)	855-448-7737	Providing preexposure prophylaxis
Substance Use Consultation	855-300-3595	Managing co-occurring substance use

Older adults can present for initial care with recently diagnosed HIV or with chronic infection reentering care. Management in older adults is often complicated by neurocognitive deficits, frailty, polypharmacy, multimorbidity, and social isolation. Therefore, older patients with HIV may require increased monitoring for medication adherence and complications. Assessing the family's health concerns can help guide care, including coordination with caregivers to clarify function and goals of care.<sup>35</sup>

## Preventing Transmission

Primary care clinicians are well positioned to effectively prevent HIV transmission by initiating and maintaining effective ART because combination ART-induced viral load suppression dramatically reduces the risk of sexual transmission to partners who are seronegative.<sup>5-8</sup> Patients should be counseled on safer sex practices to prevent sexually transmitted infections. For patients who use drugs, information on harm reduction measures and substance use disorder treatment associated with decreased HIV transmission risk, can be invaluable.<sup>36-38</sup>

Family physicians are able to offer HIV pre- and post-exposure prophylaxis for people at risk.<sup>15-18</sup> Preexposure prophylaxis is recommended for people in several risk categories, including seronegative partners of people with HIV. The U.S. Preventive Services Task Force recommendation criteria for preexposure prophylaxis have been published in *American Family Physician* (AFP; <https://www.aafp.org/afp/2019/1115/od1.html>). Postexposure prophylaxis is recommended as soon as possible and no later than 72 hours after nonoccupational exposure to potentially infectious bodily fluids from a person with HIV. AFP published a summary of the Centers for Disease Control and Prevention guidelines for postexposure prophylaxis (<https://www.aafp.org/afp/2016/0901/p392.html>). Other clinical resources are listed in Table 5.

**This article** updates previous articles on this topic by Khalsa,<sup>39</sup> Romanelli and Matheny,<sup>40</sup> and Goldschmidt, et al.<sup>41</sup>

**Data Sources:** A PubMed search was completed in Clinical Queries using the key terms HIV, AIDS, primary care, and guidelines. The search included meta analyses, randomized controlled trials, clinical trials, guidelines, and reviews. We performed specific searches on key guidelines websites, including: <https://hivinfo.nih.gov>; <https://www.cdc.gov>; and <https://www.cdc.gov/mmwr>; the Cochrane database; Essential Evidence Plus; and <https://www.aafp.org/journals/afp>. Search dates: June 3 to 5, June 27, and July 11 to 20, 2020.

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WHO GUIDELINES FOR THE

# Treatment of

# *Treponema pallidum* (syphilis)





WHO GUIDELINES FOR THE  
**Treatment of**  
***Treponema pallidum (syphilis)***

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**Web annexes available at:**

[www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/](http://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/)

**Web annex D: Evidence profiles and evidence-to-decision frameworks**

**Web annex E: Systematic reviews for syphilis guidelines**

**Web annex F: Summary of conflicts of interest**

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## ABBREVIATIONS AND ACRONYMS

AIDS	acquired immune deficiency syndrome	NAAT	nucleic acid amplification test
AMR	antimicrobial resistance	PCR	polymerase chain reaction
CI	confidence interval	PICO	population, intervention, comparator, outcome
DFA	direct fluorescent antibody	PMTCT	prevention of mother-to-child transmission
DNA	deoxyribonucleic acid	RDT	rapid diagnostic tests
DOI	declaration of interests	RPR	rapid plasma reagin
FTA-ABS	fluorescent treponemal antibody absorbed	STI	sexually transmitted infection
GDG	Guideline Development Group	TPHA	<i>Treponema pallidum</i> haemagglutination assay
GRADE	Grading of Recommendations Assessment, Development and Evaluation	TPPA	<i>Treponema pallidum</i> particle agglutination assay
GUD	genital ulcer disease	TRUST	Toluidine Red Unheated Serum Test
HIV	human immunodeficiency virus	VDRL	Venereal Diseases Research Laboratory
HPV	human papillomavirus		
HSV	herpes simplex virus		
HSV-1	herpes simplex virus type 1		
HSV-2	herpes simplex virus type 2		
ICT	immunochromatographic		
IM	intramuscular		
IV	intravenous		
MSH	Management Sciences for Health		
MSM	men who have sex with men		
MU	million units		

# WHO GUIDELINES FOR THE TREATMENT OF *TREPONEMA PALLIDUM* (SYPHILIS)

## EXECUTIVE SUMMARY

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting quality of life and causing serious morbidity and mortality. STIs have a direct impact on reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect impact through their role in facilitating sexual transmission of human immunodeficiency virus (HIV) and thus they also have an impact on national and individual economies. More than a million STIs are acquired every day. In 2012, an estimated 357 million new cases of curable STIs (gonorrhoea, chlamydia, syphilis and trichomoniasis) occurred among 15- to 49-year-olds worldwide, including 5.6 million cases of syphilis. There are an estimated 18 million prevalent cases of syphilis.

Syphilis is a bacterial STI caused by *Treponema pallidum* that results in substantial morbidity and mortality. Syphilis is transmitted through sexual contact with infectious lesions of the mucous membranes or abraded skin, via blood transfusion, or transplacentally from a pregnant woman to her fetus. Untreated, the disease lasts many years and is divided into stages. Early syphilis consists of primary syphilis, secondary syphilis and early latent syphilis, while late syphilis consists of late latent syphilis and tertiary syphilis (neurosyphilis, cardiosyphilis and gumma).

Primary syphilis classically presents as a solitary, painless chancre at the site of inoculation. However, the primary chancre may go unnoticed by patients. If untreated, the disease progresses to the secondary stage, characterized by generalized mucocutaneous lesions affecting both skin, mucous membranes and lymphnodes. The rash of secondary syphilis can vary widely and mimic other infectious and non-infectious conditions, but characteristically affects the palms and soles. The symptoms and signs of secondary syphilis spontaneously resolve, even without treatment, and if left untreated, the patient enters the latent stage.

Latent syphilis is asymptomatic, characterized by positive syphilis serology with no clinical manifestations. Latent syphilis is often divided into two phases: early latent syphilis is defined as infection for less than two years while late latent syphilis is the presence of the disease for two years or more. Sexual transmission typically occurs during primary, secondary or early latent stage infections; however, mother-to-child transmission has been documented to occur in untreated cases several years after initial maternal infection.

Mother-to-child transmission of syphilis (congenital syphilis) is usually devastating to the fetus if maternal infection is not detected and treated sufficiently early in pregnancy. The burden of morbidity and mortality due to congenital syphilis is high. In 2012, an estimated 350 000 adverse pregnancy outcomes worldwide were attributed to syphilis, including 143 000 early fetal deaths/stillbirths, 62 000 neonatal deaths, 44 000 preterm/low-birth-weight babies and 102 000 infected infants. Most untreated primary and secondary syphilis infections in pregnancy result in severe adverse pregnancy outcomes. Latent (asymptomatic) syphilis infections in pregnancy also cause serious adverse pregnancy outcomes in more than half of cases. Mother-to-child transmission of syphilis is declining globally due to increased efforts to screen and treat pregnant women for syphilis.

Syphilis diagnosis is usually based on clinical history, physical examination, laboratory testing and sometimes radiology. In most laboratory settings, the diagnosis is based upon serologic tests. These include treponemal tests that measure antibodies to infection (including *Treponema pallidum* haemagglutination assay [TPHA], *Treponema pallidum* particle agglutination assay [TPPA], fluorescent treponemal antibody absorbed [FTA-ABS]) and non-treponemal tests that are indirect markers measuring host immune response to infections (including rapid plasma reagin [RPR], Venereal Diseases Research Laboratory [VDRL], Toluidine Red Unheated Serum Test [TRUST]). Rapid treponemal tests for syphilis and dual HIV and syphilis tests are now available. These tests will increase coverage for diagnosing syphilis.

## RATIONALE FOR THE GUIDELINES

Since the publication of the WHO Guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management. These guidelines provide updated treatment recommendations for treatment of *Treponema pallidum* (syphilis) based on the most recent evidence. They form one of several modules of guidelines for specific STIs. Other modules will focus on treatments for *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhoea) and genital herpes simplex virus (genital HSV). In addition, future work will provide guidance for syphilis screening and treatment of pregnant women, STI syndromic approach, clinical management, STI prevention, and treatments of other STIs. It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols and adapt it to the local epidemiological situation and antimicrobial susceptibility data.

## OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of *Treponema pallidum*; and
- to support countries to update their national guidelines for treatment of *Treponema pallidum*.

## METHODS

These guidelines were developed following the methods outlined in the 2014 WHO handbook for guideline development. The Guideline Development Group (GDG) included international STI experts, clinicians, researchers and programme managers. The GDG prioritized questions and outcomes related to treatment of syphilis and congenital syphilis infections to include in this update, and a methodologist and a team of systematic reviewers from McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy, independently conducted systematic reviews of the effectiveness of different treatments for syphilis and congenital syphilis. The evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented to the GDG. Conflicts of interest were managed according to WHO guidelines and declared before the recommendations were discussed and finalized. Research implications were also developed by the GDG.

## RECOMMENDATIONS

The current guidelines provide treatment recommendations for *Treponema pallidum* and congenital syphilis. The recommendations summarized in Table 1 apply to all adults and adolescents (10–19 years of age), including pregnant women, people living with HIV, people who are immunocompromised and key populations, including sex workers, men who have sex with men (MSM) and transgender persons.

**Table 1. Summary of recommendations for treatment of *Treponema pallidum* and congenital syphilis**

Recommendations	Strength of recommendation and quality of evidence
<b>Early syphilis (primary, secondary and early latent syphilis of not more than two years' duration)</b>	
<b>Adults and adolescents</b>	
<b>Recommendation 1</b> In adults and adolescents with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.	<i>Strong recommendation, very low quality evidence</i>
<b>Recommendation 2</b> In adults and adolescents with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10–14 days intramuscularly. When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days, or, in special circumstances, azithromycin 2 g once orally. <i>Remarks:</i> Doxycycline is preferred over ceftriaxone due to its lower cost and oral administration. Doxycycline should not be used in pregnant women (see recommendations 3 and 4 for pregnant women). Azithromycin is an option in special circumstances only when local susceptibility to azithromycin is likely. If the stage of syphilis is unknown, follow recommendations for people with late syphilis.	<i>Conditional recommendation, very low quality evidence</i>

<b>Pregnant women</b>	
<b>Recommendation 3</b>	<i>Strong recommendation, very low quality evidence</i>
In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.	
<b>Recommendation 4</b>	<i>Conditional recommendation, very low quality evidence</i>
In pregnant women with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once daily for 10 days.	
When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days or azithromycin 2 g once orally.	
<i>Remarks:</i> Although erythromycin and azithromycin treat the pregnant women, they do not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see recommendations 9 and 10 for congenital syphilis). Ceftriaxone is an expensive option and is injectable. Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, <b>stock-outs of benzathine penicillin for use in antenatal care should be avoided.</b>	
<b>Late syphilis (infection of more than two years' duration without evidence of treponemal infection)</b>	
<b>Adults and adolescents</b>	
<b>Recommendation 5</b>	<i>Strong recommendation, very low quality evidence</i>
In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment.	
<i>Remarks:</i> The interval between consecutive doses of benzathine penicillin should not exceed 14 days.	
<b>Recommendation 6</b>	<i>Conditional recommendation, very low quality evidence</i>
In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once daily for 20 days.	
When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 30 days.	
<i>Remarks:</i> Doxycycline should not be used in pregnant women (see recommendations 7 and 8 for pregnant women).	

Pregnant women	
<b>Recommendation 7</b>  In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment.  <i>Remarks:</i> The interval between consecutive doses of benzathine penicillin should not exceed 14 days.	<i>Strong recommendation, very low quality evidence</i>
<b>Recommendation 8</b>  In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units intramuscularly once a day for 20 days  When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 30 days.  <i>Remarks:</i> Although erythromycin treats the pregnant women, it does not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see recommendations 9 and 10 for congenital syphilis). Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, <b>stock-outs of benzathine penicillin for use in antenatal care should be avoided.</b>	<i>Conditional recommendation, very low quality evidence</i>
Congenital syphilis	
Infants	
<b>Recommendation 9</b>  In infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis (including treatment within 30 days of delivery) or syphilis that was treated with non-penicillin regimens, the WHO STI guideline suggests aqueous benzyl penicillin or procaine penicillin.  Dosages: <ul style="list-style-type: none"><li>• Aqueous benzyl penicillin 100 000–150 000 U/kg/day intravenously for 10–15 days</li><li>• Procaine penicillin 50 000 U/kg/day single dose intramuscularly for 10–15 days</li></ul> <i>Remarks:</i> If an experienced venipuncturist is available, aqueous benzyl penicillin may be preferred instead of intramuscular injections of procaine penicillin.	<i>Conditional recommendation, very low quality evidence</i>
<b>Recommendation 10</b>  In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, the WHO STI guideline suggests close monitoring of the infants.  <i>Remarks:</i> The risk of transmission of syphilis to the fetus depends on a number of factors, including maternal titres from non-treponemal tests (e.g. RPR), timing of maternal treatment and stage of maternal infection, and therefore this recommendation is conditional. If treatment is provided, benzathine penicillin G 50 000 U/kg/day single dose intramuscularly is an option.	<i>Conditional recommendation, very low quality evidence</i>

## OVERVIEW OF THE GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs

### STI EPIDEMIOLOGY AND BURDEN

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting quality of life and causing serious morbidity and mortality. STIs have a direct impact on reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect impact through their role in facilitating sexual transmission of human immunodeficiency virus (HIV) and thus they also have an impact on national and individual economies. The prevention and control of STIs is an integral component of comprehensive sexual and reproductive health services that are needed to attain the related targets under Sustainable Development Goal (SDG) No. 3 (Ensure healthy lives and promote well-being for all at all ages), including: target 3.2 – to end preventable deaths of newborns and children under 5 years of age; target 3.3 – to end the epidemics of AIDS and other communicable diseases; target 3.4 – to reduce premature mortality from noncommunicable diseases and promote mental health and well-being; target 3.7 – to ensure universal access to sexual and reproductive health-care services; and target 3.8 – to achieve universal health coverage.

Worldwide, more than a million curable STIs are acquired every day. In 2012, there were an estimated 357 million new cases of curable STIs among adults aged 15–49 years worldwide: 131 million cases of chlamydia, 78 million cases of gonorrhoea, 6 million cases of syphilis and 142 million cases of trichomoniasis (1). The prevalence of some viral STIs is similarly high, with an estimated 417 million people infected with herpes simplex virus type 2 (HSV-2) (2), and approximately 291 million women harbouring human papillomavirus (HPV) at any point in time (3). The burden of STIs varies by region and gender, and is greatest in resource-poor countries.

When left undiagnosed and untreated, curable STIs can result in serious complications and sequelae, such as pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, fetal loss and congenital infections. In 2012, an estimated 930 000 maternal syphilis infections resulted in 350 000 adverse pregnancy outcomes, including stillbirths, neonatal deaths, preterm births and infected infants (4). Curable STIs accounted for the loss of nearly 11 million disability-adjusted life years (DALYs) in 2010 (5). The psychological consequences of STIs include stigma, shame and loss of self-worth. STIs have also been associated with relationship disruption and gender-based violence (6).

Both ulcerative and non-ulcerative STIs are associated with a several-fold increased risk of transmitting or acquiring HIV (7, 8). Infections causing genital ulcers are associated with the highest HIV transmission risk; in addition to curable ulcer-causing STIs (e.g. syphilis and chancroid), highly prevalent HSV-2 infections substantially increase that risk (9). Non-ulcerative STIs, such as gonorrhoea, chlamydia and trichomoniasis, have been shown to increase HIV transmission through genital shedding of HIV (10). Treating STIs with the right medicines at the right time is necessary to reduce HIV transmission and improve sexual and reproductive health (11). Efforts should therefore be taken to strengthen STI diagnosis and treatment.

### WHY NEW GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs?

Since the publication of the World Health Organization (WHO) Guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management. Indeed, 88% of countries have updated their national STI guidelines or recommendations since 2006 (12). Updated global guidance reflecting the most recent evidence and expert opinion is therefore needed to assist countries to incorporate new developments into an effective national approach to the prevention and treatment of STIs.

There is an urgent need to update global treatment recommendations to effectively respond to the changing antimicrobial resistance (AMR) patterns of STIs, especially for *Neisseria gonorrhoeae*. Effective treatment protocols that take into account global and local resistance patterns are essential to reduce the risk of further development of AMR. High-level gonococcal resistance to quinolones, a previously recommended first-line treatment, is widespread and decreased susceptibility to the extended-spectrum (third-generation) cephalosporins, another first-line treatment for gonorrhoea, is on the rise (13). Low-level resistance to Trichomonas vaginalis has also been reported for nitroimidazoles, the only available treatment. Resistance to azithromycin has been reported in some strains of *Treponema pallidum* and treatment failures have been reported for tetracyclines and macrolides in the treatment of *Chlamydia trachomatis* (14, 15). A WHO STI expert consultation recommended updating the WHO 2003

guidelines for the first- and second-line treatments for *C. trachomatis*, increasing the dosage of ceftriaxone to 250 mg for treatment of *N. gonorrhoeae* with continued monitoring of antimicrobial susceptibility, and consideration of whether azithromycin (2 g, single dose) should be recommended in early syphilis (16).

The epidemiology of STIs is changing, with viral pathogens becoming more prevalent than bacterial etiologies for some conditions; this means that updated information is required to inform locally appropriate prevention and treatment strategies. An increasing proportion of genital ulcers are now due to viral infections as previously common bacterial infections, such as chancroid, approach elimination in many countries (16, 17). As recommended during the STI expert consultation, treatment guidelines for genital ulcer disease (GUD) should be updated to include HSV-2 treatment and a longer treatment duration for HSV-2 should be explored. In addition, suppressive therapy for HSV-2 should be considered in areas with high HIV prevalence (16). The chronic, lifelong nature of viral infections also requires that renewed attention be paid to developing effective prevention strategies, including expanding accessibility to available vaccines for HPV and development of new vaccines for HSV-2.

In the 2003 WHO guidelines, a syndromic approach was recommended for the management of STIs. The approach guides the diagnosis of STIs based on identification of consistent groups of symptoms and easily recognized signs and indicates treatment for the majority of organisms that may be responsible for producing the syndrome. The syndromic management algorithms need to be updated in response to the changing situation. In addition to changes to the GUD algorithm, other syndromes need to be re-evaluated, particularly vaginal discharge. The approach to syndromes for key populations also needs to be updated. For example, addition of a syndromic management algorithm for anorectal infections in men who have sex with men (MSM) and sex workers is urgently needed since a substantial number of these infections go unrecognized and untreated in the absence of guidelines (16).

New rapid, point-of-care diagnostic tests (POCTs) are changing STI management. Rapid syphilis diagnostic tests are now widely available, making syphilis screening more widely accessible and allowing for earlier initiation of treatment for those who test positive. Efforts are under way to develop POCTs for other STIs that will augment syndromic management of symptomatic cases and increase the ability to identify asymptomatic infections (12). Updated guidelines are needed that incorporate rapid tests into syndromic management of STIs and provide algorithms for testing and screening (16).

Although recent technological advances in diagnostics, therapeutics, vaccines and barrier methods offer better opportunities for the prevention and care of STIs, access to these technologies is still limited, particularly in areas where the burden of infection is highest. For optimal effectiveness, global guidelines for the management of STIs need to include approaches for settings with limited access to modern technologies, as well as for settings in which these technologies are available.

It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols, adapting this guidance to the local epidemiological situation and antimicrobial susceptibility data. Standardization ensures that all patients receive adequate treatment at every level of health-care services, optimizes the training and supervision of health-care providers and facilitates procurement of medicines. It is recommended that national guidelines for the effective management of STIs be developed in close consultation with local STI, public health and laboratory experts.

## APPROACH TO THE REVISION OF STI GUIDELINES

To ensure effective treatment for all STIs, WHO plans a phased approach to updating the STI guidelines to address a range of infections and issues. Four phases have been proposed by the WHO STI Secretariat and agreed upon by the STI Guideline Development Group (GDG) members (see Annex A for members of these groups). Table 2 summarizes the proposed phases and timeline.

**Table 2: Phases for development of the STI guidelines**

Phases	Topics	Timeframe
Phase 1	Treatment of specific STIs: <i>Chlamydia trachomatis</i> (chlamydia), <i>Neisseria gonorrhoeae</i> (gonorrhoea), HSV-2 (genital herpes) and <i>Treponema pallidum</i> (syphilis)  Syphilis screening and treatment of pregnant women  STI syndromic approach  Clinical management package	November 2013 – April 2016    May 2016 – December 2017
Phase 2	STI prevention: condoms, behaviour change communication, biomedical interventions and vaccines	2017–2018
Phase 3	Treatment of specific STIs and reproductive tract infections (RTIs) not addressed in Phase 1: <i>Trichomonas vaginalis</i> (trichomoniasis), bacterial vaginosis, <i>Candida albicans</i> (candidiasis), <i>Hemophilus ducreyi</i> (chancroid), <i>Klebsiella granulomatis</i> (donovanosis), human papillomavirus (HPV; genital warts/cervical cancer), <i>Sarcoptes scabiei</i> (scabies) and <i>Phthirus pubis</i> (pubic lice)	2017–2018
Phase 4	STI laboratory diagnosis and screening	2017–2018

Phase 1 will focus on treatment recommendations for specific STIs as well as other important and urgent STI issues. Recommendations for the treatment of specific infections will be developed and published as independent modules:

- *Chlamydia trachomatis* (chlamydia)
- *Neisseria gonorrhoeae* (gonorrhoea)
- HSV-2 (genital herpes)
- *Treponema pallidum* (syphilis)
- Syphilis screening and treatment of pregnant women.

In addition, guidelines for the STI syndromic approach and a clinical management package will be developed later in Phase 1. Phase 2 will focus on guidelines for STI prevention. The independent Phase 1 and 2 modules will later be consolidated into one document and published as comprehensive WHO guidelines on STI case management. Phase 3 will address treatment of additional infections, including *Trichomonas vaginalis* (trichomoniasis), bacterial vaginosis, *Candida albicans* (candidiasis), *Hemophilus ducreyi* (chancroid), *Klebsiella granulomatis* (donovanosis), HPV (genital warts/cervical cancer), *Sarcoptes scabiei* (scabies) and *Phthirus pubis* (pubic lice). Phase 4 will provide guidance on laboratory diagnosis and screening of STIs.

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# 01

## INTRODUCTION

### 1.1 EPIDEMIOLOGY, BURDEN AND CLINICAL CONSIDERATIONS

Syphilis is a bacterial sexually transmitted infection (STI) caused by *Treponema pallidum*. It results in substantial morbidity and mortality. WHO estimates that 5.6 million new cases of syphilis occurred among adolescents and adults aged 15–49 years worldwide in 2012 with a global incidence rate of 1.5 cases per 1000 females and 1.5 per 1000 males. The estimated 18 million prevalent cases of syphilis in 2012 translates to a global prevalence of 0.5% among females and 0.5% among males aged 15–49 years, with the highest prevalence in the WHO African Region (1).

Mother-to-child transmission may occur if the expectant mother has syphilis. Mother-to-child transmission of syphilis (congenital syphilis) is usually devastating to the fetus in cases where maternal infection is not detected and treated sufficiently early in pregnancy. The burden of morbidity and mortality due to congenital syphilis is high. In 2012, an estimated 350 000 adverse pregnancy outcomes worldwide were attributed to syphilis, including 143 000 early fetal deaths/stillbirths, 62 000 neonatal deaths, 44 000 preterm/low-birth-weight babies and 102 000 infected infants. There is also an increase in mother-to-child transmission of HIV among pregnant women co-

infected with syphilis and HIV. Untreated primary and secondary syphilis infections in pregnancy typically result in severely adverse pregnancy outcomes, including fetal deaths in a substantial proportion of cases. Latent syphilis infections in pregnancy result in serious adverse pregnancy outcomes in more than half of cases. The burden of disease is highest in low- and middle-income countries, particularly in the WHO African Region (2).

Congenital syphilis is preventable, however, and elimination of mother-to-child transmission of syphilis can be achieved through implementation of effective early screening and treatment strategies for syphilis in pregnant women (3). The fetus can be easily cured with treatment, and the risk of adverse outcomes to the fetus is minimal if the mother receives adequate treatment during early pregnancy – ideally before the second trimester. There are indications that mother-to-child transmission of syphilis is beginning to decline globally due to increased efforts to screen and treat pregnant women for syphilis.

### CLINICAL PRESENTATION

Syphilis is transmitted through sexual contact with infectious lesions of the mucous membranes or abraded skin, via blood transfusion, or transplacentally from a pregnant woman to her fetus. Untreated, the disease lasts many years and is divided into stages. Early syphilis consists of primary syphilis, secondary syphilis and early latent syphilis, while late syphilis consists of late latent syphilis and tertiary syphilis.

Primary syphilis classically presents as a solitary, painless chancre at the site of inoculation, usually in the vagina, penis or anus (but it may be extra-genital), after a mean incubation period of 21 days (range: 9–90 days). The primary lesion begins as a raised papule and ulcerates before healing within 3 to 10 weeks, with or without treatment. The primary chancre may go unnoticed by patients. If untreated, the disease progresses to the secondary stage, four to eight weeks after the appearance of the primary lesion.

Secondary syphilis is characterized by generalized mucocutaneous lesions affecting both skin and mucous membranes. The rash of secondary syphilis can vary widely and mimic other infectious or non-infectious conditions, but characteristically affects the palms and soles. The rash is often symmetrical and non-itchy, but may have several manifestations and can be minimal enough to be overlooked. In warm and moist areas of the body, such as the anus and labia, large white or grey raised lesions develop as a result of the spread of the treponemes from the primary lesion.

These are known as condylomata lata. The lesions of the skin and mucous membranes may be associated with non-specific constitutional symptoms of malaise, fever and lymphadenopathy. The symptoms and signs of secondary syphilis spontaneously resolve, even without treatment, and if left untreated, the patient enters the latent stage.

Latent syphilis is characterized by positive syphilis serology with no clinical symptoms or signs. Latent syphilis is often categorized in two phases: early latent syphilis is defined as infection for less than two years and late latent syphilis is the presence of the disease for two years or more. The treatment of latent syphilis is different for the early and late phases. Patients with unknown duration of infection should be treated for late latent syphilis. Sexual transmission typically occurs only during primary, secondary and early latent infection. Mother-to-child transmission, however, has been documented to occur up to several years after initial infection.

If left untreated, most patients will remain in the latent stage. Approximately 25% will develop the late clinical sequelae of tertiary syphilis (4), which can affect any organ system up to 30 years or more after infection. The main manifestations of tertiary syphilis are neurological disease (neurosyphilis), cardiovascular disease (cardiosyphilis) and gummatous lesions (gumma).

Neurosyphilis can occur at any stage of syphilis infection, even in the first few months. Early neurological manifestations include acute changes in mental status, meningitis, stroke, cranial nerve dysfunction and auditory or ophthalmic and ocular abnormalities. Late neurosyphilis occurs 10–30 years or more after infection and is characterized by tabes dorsalis and general paresis.

The most common manifestation of congenital syphilis is second or third trimester fetal loss or premature labour. Thus, serologic testing for syphilis should be performed for all mothers with stillborn infants, to document evidence of syphilis. In most countries, it is estimated that the majority of congenital syphilis cases result in syphilitic stillbirths, and these cases are often not recognized as having been caused by syphilis. Infants born to mothers with positive syphilis serology should be examined for signs and symptoms of early congenital syphilis, including bullous rash, rhinitis, laryngitis, lymphadenopathy, hepatosplenomegaly, osteochondritis, periostitis, meningitis and chorioretinitis. The signs of late congenital syphilis infection in children over the age of 2 years include inflammatory manifestations affecting the eyes, ears and joints, as well as skeletal malformations and

stigmata resulting from developmental damage during the early stages of syphilis. However, it is important to keep in mind that many infants with syphilis infection will not have obvious clinical signs or symptoms.

#### BOX 1. THE WHO GLOBAL SURVEILLANCE CASE DEFINITION FOR CONGENITAL SYPHILIS

- A stillbirth, live birth or fetal loss at greater than 20 weeks of gestation or more than 500 g to a syphilis seropositive mother without adequate syphilis treatment; or
- A stillbirth, live birth or child under 2 years of age with clinical (as above) or microbiological evidence of syphilis infection. The microbiological evidence of congenital syphilis includes any one of the following:
  - demonstration by dark-field microscopy or direct fluorescent antibody test of the presence of *T. pallidum* in the umbilical cord, the placenta, nasal discharge or skin lesion materials;
  - detection of *T. pallidum*-specific IgM;
  - infant with a positive non-treponemal serology titre at least four-fold higher than the mother's titre.

Source: Global guidance on criteria and processes for validation: elimination of mother-to-child transmission (EMTCT) of HIV and syphilis. Geneva: World Health Organization; 2014 (5).

#### LABORATORY DIAGNOSIS

Syphilis diagnosis is based on the patient's history, physical examination, laboratory testing and sometimes radiology. The available laboratory tests for diagnosis of syphilis include direct detection methods (i.e. dark-field microscopy, direct fluorescent antibody test and nucleic acid amplification test), serology (treponemal and non-treponemal tests), and examination of cerebrospinal fluids (6).

## DIRECT DETECTION METHODS

Direct detection methods require exudates from lesions of primary, secondary or early congenital syphilis, and need careful collection of samples.

Dark-field microscopy demonstrating treponemes with characteristic morphology and motility in lesion exudate or tissue is the most specific method for diagnosis of the early stages of syphilis. The dark-field examination must be performed immediately after specimen collection from primary chancres, moist secondary lesions or lymph nodes or from mucocutaneous lesions in newborns. Dark-field microscopy requires specialized equipment and a trained, experienced microscopist, and is therefore usually limited to specialized laboratories. Dark-field microscopy is highly specific, therefore the presence of characteristic spirochetes is diagnostic of an active infection. Its sensitivity, however, is less than 50%, so a negative result does not exclude syphilis. Although dark-field microscopy is one of the simplest and most reliable methods for the direct detection of *T. pallidum*, its availability is increasingly limited.

The direct fluorescent antibody (DFA) test uses a fluorescence microscope to detect spirochetes that have been stained with fluorescein-labelled anti-*T. pallidum* globulin. Specimens are obtained in the same way as for dark-field microscopy, but the fluorescein-stained organisms are easier to detect and are not likely to be confused with other organisms, leading to a higher sensitivity and specificity for the DFA test. However, specialized equipment is required and the specific fluorescein conjugate is not commercially available in most countries.

Nucleic acid amplification tests (NAATs) directly detect *T. pallidum* DNA by polymerase chain reaction (PCR) from specimens of any lesion exudate, tissue or body fluid. The sensitivity varies according to the specific PCR assay; most assays can detect approximately 10 organism equivalents, although some can detect one organism per PCR reaction. Commercial PCR tests for *T. pallidum* are not yet commercially available and therefore are relatively costly compared with other tests used to diagnose syphilis. For studies with testing done in well-equipped laboratories, multiplex PCR assays have been developed for detection of the most common causes of genital ulcers, including syphilis, herpes simplex virus and *H. ducreyi* (chancroid).

## SYPHILIS SEROLOGY

There are two types of serological tests for syphilis: non-treponemal and treponemal. A presumptive diagnosis of syphilis requires a positive result from at least one of these types of tests. A confirmed diagnosis requires positive results from both types of serologic tests.

Serum is the specimen of choice for serological testing, although plasma can be used in some non-treponemal serological tests. Cerebrospinal fluid is used to diagnose congenital and tertiary syphilis and when neurological symptoms are present.

The most widely available non-treponemal tests are the microscopic Venereal Diseases Research Laboratory (VDRL) and the macroscopic rapid plasma reagins (RPR) tests. These tests detect anti-lipid immunoglobulin M or G (IgM or IgG) antibodies. Since these antibodies can also be produced in other diseases, non-treponemal tests are not highly specific for syphilis and can give false-positive results in conditions such as acute febrile viral infections and some chronic autoimmune diseases. Most false-positive results have low titres of less than 1 : 4. Non-treponemal tests may be negative for up to four weeks after the lesion of primary syphilis first appears and can be negative in late latent syphilis; additionally in primary and secondary syphilis, these tests may be false negative due to a prozone reaction (i.e. interference by high concentrations of antibodies in a specimen, which can be uncovered with dilution and retesting). In primary syphilis, repeated testing at two and four weeks may be required to exclude syphilis when suspect lesions are present. A negative non-treponemal test at three months after onset of the primary chancre virtually excludes the diagnosis of syphilis.

Non-treponemal tests may be qualitative or quantitative. Quantitative non-treponemal test titres can be used to monitor response to treatment. Titres are expected to decrease following effective treatment and increase in untreated active infection. A four-fold change or higher in titre, equivalent to a change of at least two dilutions (e.g. from 1 : 16 to 1 : 4 for effective positive response to treatment, or from 1 : 8 to 1 : 32 for continued active infection) is considered a significant difference between two sequential tests using the same method (e.g. VDRL or RPR) and preferably by the same laboratory. Titres that differ by only one dilution (e.g. 1 : 8 versus 1 : 4 or 1 : 2 versus 1 : 1) are not considered significant and may only represent differences in laboratory interpretation).

Treponemal tests include the *Treponema pallidum* haemagglutination assay (TPHA), the *Treponema pallidum* particle agglutination assay (TPPA) and the fluorescent treponemal antibody absorbed (FTA-ABS) tests. These tests are highly specific because they detect antibodies against treponemal-specific antigens; however, they do not differentiate venereal syphilis from endemic syphilis (the latter includes yaws and pinta). Classically, one of these tests is used as a confirmatory test following a positive non-treponemal test. Treponemal tests usually remain positive (85%) for the patient's lifetime, regardless of treatment. Thus, a positive treponemal test does not distinguish between active infection and infection that has been previously treated.

All live or stillborn infants of seropositive mothers should be examined for evidence of congenital syphilis. Live-born infants should be examined and tested at birth and at monthly intervals for three months until it is confirmed that serological tests in the infant are, and remain, negative. Antibodies can be passively transmitted from the mother, complicating the interpretation of laboratory results in neonates, but usually disappear within three to four months after birth. However, maternal antibodies can sometimes persist for up to 18 months. In such cases, repeat testing with titration should be carried out and if a four-fold or greater increase in titre of a non-treponemal or treponemal test is detected, the baby should be treated for congenital syphilis.

#### RAPID DIAGNOSTIC TESTS

In the past decade, a number of point-of-care rapid diagnostic tests (RDTs) for treponemal antibodies in syphilis infection have been developed. RDTs provide treponemal antibody results in 10–15 minutes and can be performed in any setting since they do not require refrigerated storage or laboratory equipment. The sensitivity of the RDTs ranges from 85% to 98% and the specificity from 93% to 98%, compared to the TPHA or TPPA as reference standards. In general, RDTs with higher sensitivities tend to have lower specificities and vice versa.

Most of the initial range of RDTs use *T. pallidum* antigens to detect treponema-specific antibodies. Many of the tests use immunochromatographic strips, which work by having a test strip impregnated with treponemal antigens that react with antibodies to syphilis in whole blood or serum. The tests work on the same principle as the specific treponemal tests described above, thus a positive result does not distinguish between active and previously treated infections.

More recently, tests that can detect antibodies against cardiolipin-like materials have been developed that work on the same principle as other non-treponemal tests. They are available in combination with the treponemal RDTs, providing both a screening (RPR/VDRL equivalent) and confirmatory (TPHA/TPPA equivalent) component. However, these dual RDTs have not yet been sufficiently evaluated or field-tested to be recommended.

#### 1.2 RATIONALE FOR NEW RECOMMENDATIONS

Review and reassessment of the guidelines for treatment of syphilis is needed, taking into account recent evidence on the effectiveness and antimicrobial susceptibility patterns of azithromycin. Benzathine penicillin has been the recommended treatment for syphilis for more than 70 years. Doxycycline is recommended as an alternative treatment for penicillin-allergic, non-pregnant patients. Some studies suggest that azithromycin may be equivalent to benzathine penicillin for treatment of early syphilis. Azithromycin has the added advantage of single-dose oral administration and should be assessed as a possible alternative treatment for penicillin-allergic pregnant patients. However, those advantages need to be weighed against the increasing number of reports of *T. pallidum* azithromycin resistance. Other options for treating penicillin-allergic patients should also be explored, such as desensitization and injectable daily ceftriaxone.

The WHO Guidelines for the management of sexually transmitted infections, published in 2003 (7), recommend early screening and treatment of pregnant women with syphilis, ideally prior to the second trimester of pregnancy, to avoid any fetal complications. In addition, the 2003 WHO STI guidelines recommended treatment for early and late congenital syphilis. Based on this recommendation, it is important for the health-care provider to make a diagnosis and to differentiate early and late congenital syphilis. Diagnosis of congenital syphilis remains a challenge because it requires clinical acumen and availability of laboratory tests. Given these challenges, countries have expressed the need for diagnostic guidelines and treatment recommendations based not only on clinical signs and laboratory tests for congenital syphilis, but also on maternal syphilis serostatus and treatment.

### 1.3 OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of infection with *Treponema pallidum*; and
- to support countries to update their national guidelines for treatment of *Treponema pallidum*.

### 1.4 TARGET AUDIENCE

These guidelines are primarily intended for health-care providers at all levels (primary, secondary and tertiary) of the health-care system involved in the treatment and management of people with STIs in low-, middle- and high-income countries. They are also intended for individuals working in sexual and reproductive health programmes, such as HIV/AIDS, family planning, maternal and child health and adolescent health, to ensure appropriate STI diagnosis and management.

The guidelines are also useful for policy-makers, managers, programme officers and other professionals in the health sector who are responsible for implementing STI management interventions at regional, national and subnational levels.

### 1.5 STRUCTURE OF THE GUIDELINES

These guidelines provide evidence-based recommendations for the treatment of specific clinical conditions caused by *T. pallidum*. These guidelines provide direction for countries as they develop national treatment recommendations; however, national guidelines should also take into account the local pattern of antimicrobial resistance (AMR), as well as health service capacity and resources.

Updated treatment recommendations based on the most recent evidence are included for the most important common conditions caused by *T. pallidum*. Recommendations were not updated for rare conditions including neurosyphilis and tertiary syphilis (gumma and cardiovascular syphilis) for which no new information became available since the 2003 WHO STI guidelines were issued.

Treatment recommendations for the following conditions caused by *T. pallidum* are included in these guideline:

- early latent syphilis
- late latent syphilis
- congenital syphilis.

# 02

## METHODS

These guidelines were developed following the methods outlined in the 2014 edition of the WHO handbook for guideline development (8) (see Annex B for a detailed description).

### 2.1 GUIDELINE DEVELOPMENT GROUP (GDG)

To update the WHO guidelines for the prevention, treatment and management of STIs, a GDG was established, comprising 33 international STI experts, including clinicians, researchers and programme managers (Annex A). A core subgroup to focus on the guidelines related to syphilis was created within the GDG, to provide more intensive feedback throughout the process (Annex A). The GDG participated in meetings and teleconferences to prioritize the questions to be addressed, discuss the evidence reviews and finalize the recommendations.

Additional sub-working group teleconferences were organized to review the methodology and results of systematic reviews and to discuss and finalize the evidence reviews and recommendations. The GDG reviewed and approved the final version of the guidelines.

### 2.2 QUESTIONS AND OUTCOMES

In December 2013, the first GDG meeting was held to identify and agree on the key PICO (population, intervention, comparator, outcome) questions that formed the basis for the systematic reviews and the recommendations. Following this meeting, a survey of GDG members was conducted to prioritize the questions and outcomes according to clinical relevance and importance. Nine PICO questions were identified for the update on the treatment of early and late syphilis and congenital syphilis (see Annex B). These questions pertained to adults and other special populations, namely: adolescents; pregnant women; people living with HIV; populations at high risk of acquiring and transmitting STIs, such as men who have sex with men (MSM), transgender persons and sex workers; and infants and children below the age of 2 years (i.e. the questions on congenital syphilis). Only outcomes that were ranked as critical or important to patients and decision-making were included: serological response and clinical cure, transmission to partner, antimicrobial resistance (AMR), compliance, HIV transmission or acquisition, STI complications and adverse effects (including maternal and fetal effects in pregnant women) (see Annex B).

### 2.3 REVIEWS OF THE EVIDENCE

The systematic reviews for each priority question were conducted by McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy. Evidence for desirable and undesirable outcomes, patient values and preferences, resources, acceptability, equity and feasibility were reviewed from published and unpublished literature. Comprehensive searches for previously conducted systematic reviews, randomized controlled trials and non-randomized studies were performed up to April 2015. Additional searches were conducted to identify studies on patient values and preferences (e.g. qualitative research designs) and resources (e.g. cost-effectiveness studies). Two members of the Systematic Review Team screened studies, extracted and analysed the data, and assessed the quality/certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>1</sup>

<sup>1</sup> For more information, see: <http://www.gradeworkinggroup.org/>

The quality/certainty of the evidence was assessed at four levels:

- **High** – We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** – We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** – Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low** – We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

In addition, the direct costs of medicines were estimated using the 2014 edition of the Management Sciences for Health (MSH) International drug price indicator guide (9). References for all the reviewed evidence are listed in Annex C. All evidence was summarized in GRADE evidence profiles and in evidence-to-decision frameworks (see Web annexes D and E).

## 2.4 MAKING RECOMMENDATIONS

Recommendations were developed during a second meeting of the GDG in October 2015, which was facilitated by two co-chairs, one with expertise in GRADE and the other with clinical STI expertise. The methodologist presented the GRADE evidence profiles and evidence-to-decision frameworks at the meeting. When formulating the recommendations, the GDG considered and discussed the desirable and undesirable effects of the interventions, the value placed on the outcomes, the associated costs and use of resources, the acceptability of the interventions to all stakeholders (including people affected by STIs), the impact on health equity and the feasibility of implementation. Treatments were judged according to the above criteria and final decisions and guideline recommendations were agreed. The discussion was facilitated by the co-chairs with the goal of reaching consensus across the GDG. Disagreements among the GDG members were noted in the evidence-to-decision framework for each judgement. In the case of failure to reach consensus for a recommendation, the planned procedure was for the GDG to take a vote and record the results. However, no votes were taken because the GDG reached consensus during discussion for all of the recommendations. Following the meeting, the recommendations were finalized via teleconference and final approval was obtained from all GDG members electronically. These guidelines were subsequently written up in full and then peer reviewed. The External Review Group approved the methods and agreed with the recommendations made by the GDG (members are listed in Annex A).

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations are presented using the wording “The WHO STI guideline recommends...”, while conditional recommendations are worded as “The WHO STI guideline suggests...” throughout the guidelines. The implications of the differing strengths of recommendations for patients, clinicians and policy-makers are explained in detail in Table 3.

**Table 3. Implications of strong and conditional recommendations using the GRADE approach**

Implications	Strong recommendation “The WHO STI guideline recommends...”	Conditional recommendation “The WHO STI guideline suggests...”
For patients	<p>Most individuals in this situation would want the recommended course of action, and only a small proportion would not.</p> <p>Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</p>	<p>The majority of individuals in this situation would want the suggested course of action, but many would not.</p>
For clinicians	<p>Most individuals should receive the recommended course of action.</p> <p>Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.</p>	<p>Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences.</p> <p>Decision aids may be useful to help individuals make decisions consistent with their values and preferences.</p>
For policy-makers	<p>The recommendation can be adopted as policy in most situations.</p>	<p>Policy-making will require substantial debate and involvement of various stakeholders.</p>

## 2.5 MANAGEMENT OF CONFLICTS OF INTEREST

Management of conflicts of interest was a key priority throughout the process of guideline development.

WHO guidelines for declaration of interests

(DOI) for WHO experts were implemented (10).

DOI statements were obtained from all GDG members prior to assuming their roles in the group. At the GDG meetings (December 2013 and October 2015), the members disclosed their interests, if any, at the beginning of the meetings. The DOI statements are summarized in Web annex F.

After analysing each DOI, the STI team concluded that no member had financial or commercial interests related to STI treatment. Other notified interests were minor; they were either not related to STI or were non-commercial grants or interests. The STI team concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the guideline development process. Therefore, options for conditional participation, partial or total exclusion of any GDG member were not discussed.

# 03

## DISSEMINATION, UPDATING AND IMPLEMENTATION OF THE GUIDELINES

United Nations Programme on HIV/AIDS (UNAIDS), nongovernmental organizations (NGOs) and other agencies implementing sexual and reproductive health and STI services – to ensure that the new recommendations are integrated and implemented in sexual and reproductive health, family planning, and maternal, neonatal, child and adolescent health services. Reference to this document will be made within other relevant WHO guidelines. These guidelines will also be disseminated at major conferences related to STIs and HIV and the aforementioned programme areas.

### 3.2 UPDATING THE STI GUIDELINES AND USER FEEDBACK

A system of monitoring relevant new evidence and updating the recommendations as new findings become available will be established within a year of implementing the guidelines. An electronic follow-up survey of key end-users of the STI guidelines will be conducted after the release of the guidelines. The results of the survey will be used to identify challenges and barriers to the uptake of the guidelines, to evaluate their usefulness for improving service delivery, and to identify topics or gaps in treatment that need to be addressed in future editions.

### 3.1 DISSEMINATION

The guidelines will be made available as a printed publication, as a download on the website of the WHO Department of Reproductive Health and Research (where there will also be links to all supporting documentation)<sup>2</sup>, and in the WHO Reproductive Health Library (RHL)<sup>3</sup>. The recommendations will also be available in a guideline application ("app") created with the GRADEpro GDT software. The guidelines will be announced in the next edition of the RHL newsletter and in the Reproductive Health and Research departmental newsletter, and other relevant organizations will be requested to copy the announcement in their respective newsletters.

WHO headquarters will work with WHO's regional offices and country offices to ensure that countries receive support in the adaptation, implementation and monitoring of these guidelines using the WHO Department of Reproductive Health and Research guidance on Introducing reproductive health guidelines and tools into national programmes (11). All levels of WHO (headquarters, regional offices and countries) will work with regional and national partners – including the United Nations Population Fund (UNFPA), the United Nations Children's Fund (UNICEF), the Joint

### 3.3 IMPLEMENTATION OF THE WHO GUIDELINES FOR THE TREATMENT OF *T. PALLIDUM* (SYPHILIS)

#### ADAPTATION, IMPLEMENTATION AND MONITORING

These guidelines provide recommendations for treatment of syphilis based on the best global evidence available at the time of compilation. However, the epidemiology and AMR of STIs vary by geographical location and are constantly changing, sometimes rapidly. It is recommended that countries conduct good quality studies to gather the information needed to adapt these guidelines to the local STI situation as they update their national guidelines. In areas lacking local data as a basis for adaptation, the recommendations in these guidelines can be adopted as presented.

For further guidance on adaptation, implementation and monitoring of national guidelines please refer to Introducing WHO's reproductive health guidelines and tools into national programmes: principles and processes of adaptation and implementation (11).

<sup>2</sup> These guidelines and all supporting documents will be available at: [www.who.int/reproductivehealth/publications/stis/syphilis-treatment-guidelines/en/](http://www.who.int/reproductivehealth/publications/stis/syphilis-treatment-guidelines/en/)

<sup>3</sup> RHL is available at: <http://apps.who.int/rhl/en/>

In adapting the guidelines for national use, recommended treatments should have an efficacy of at least 95%. The criteria to be considered for the selection of medicines are listed in Box 2. Recommended medicines should meet as many of the criteria as possible, taking into account local availability, efficacy, route and frequency of administration.

#### **BOX 2. CRITERIA FOR THE SELECTION OF MEDICINES FOR THE TREATMENT OF STIS**

- High efficacy (at least 95% cure rate)
- High quality (potent active ingredient)
- Low cost
- Low toxicity levels
- Organism resistance unlikely to develop or likely to be delayed
- Single dose
- Oral administration
- Not contraindicated for pregnant or lactating women

Appropriate medicines should be included in the national essential medicines lists.

When selecting medicines, consideration should be given to the competencies and experience of health-care providers.

Budgeting for medicines is critical. If the national ministry of health does not provide medicines for free and the patient cannot afford to buy the medicines, then there will essentially be no possibility of curtailing the spread of infection and the occurrence of complications. At the national level it is important that decision-makers, politicians and fiscal controllers understand the need to subsidize STI medicines. Low-cost STI medicines can be obtained through international vendors of generic products, non-profit organizations with procurement schemes such UNICEF, UNFPA and UNHCR, and through joint medicine procurement schemes. By way of such schemes, national programmes can join other national programmes to jointly procure medicines, thus reducing the overall costs by sharing the overhead costs and taking advantage of discounts for purchasing in bulk. Placing STI medicines on national lists of essential medicines increases the likelihood of achieving a supply of these medicines at low cost.

#### **IDENTIFYING AND PROCURING STI MEDICINES**

It is important not only to identify medicines that will be recommended as first-line treatment for STIs but also the estimated quantities of medicines that will be required. Quantifying medication needs is important in order to estimate costs, to reconcile financial requirements with available budget, and to make orders in advance so that the unit and freight costs can be minimized.

In order to estimate the quantity of medicines needed, it will be necessary to review the medicines that are recommended for treatment, their unit prices, the quantity required per treatment and the epidemiological information on the prevalence of infection. One can estimate medicine needs by multiplying the estimated number of cases by the total quantity of medicine specified for treatment of one case. These figures can be derived from health centres providing care but they must be verified to avoid wasteful over-ordering.

# 04

## RECOMMENDATIONS FOR TREATMENT OF SYPHILIS

The first eight recommendations (in sections 4.1 and 4.2) apply to adults and adolescents (10–19 years of age), including people living with HIV, key populations (including sex workers, men who have sex with men and transgender persons), and pregnant women. Specific recommendations have also been developed for congenital syphilis caused by *T. pallidum* – recommendations 9 and 10 apply to infants (see section 4.3).

### **4.1 EARLY SYPHILIS (PRIMARY, SECONDARY AND EARLY LATENT SYPHILIS OF NOT MORE THAN TWO YEARS' DURATION)**

#### **ADULTS AND ADOLESCENTS RECOMMENDATION 1**

In adults and adolescents with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.

*Strong recommendation, very low quality evidence*

#### **RECOMMENDATION 2**

In adults and adolescents with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10–14 days intramuscularly.

*Conditional recommendation, very low quality evidence*

When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days, or, in special circumstances, azithromycin 2 g once orally.

*Conditional recommendation, very low quality evidence*

**Remarks:** Doxycycline is preferred over ceftriaxone due to its lower cost and oral administration. Doxycycline should not be used in pregnant women (see recommendations 3 and 4 for pregnant women). Azithromycin is an option in special circumstances only when local susceptibility to azithromycin is likely. If the stage of syphilis is unknown, recommendations for people with late syphilis should be followed.

#### **SUMMARY OF THE EVIDENCE**

Overall, there was very low quality evidence for outcomes after treatment of early syphilis. Evidence was gathered from 7 randomized and 18 non-randomized studies, each of which included one or two groups evaluating benzathine penicillin G, procaine penicillin, ceftriaxone, azithromycin and doxycycline (with or without tetracycline). Although not captured in published studies, most treatments today are based on historical and successful use of benzathine penicillin G and procaine penicillin. The number of serological cures achieved with benzathine penicillin G 2.4 million units (MU) provided as a single dose intramuscularly (IM) was estimated on average as 840 per 1000 people with early syphilis. When compared to this single dose of benzathine penicillin G, the evidence suggests little to no difference in the numbers of serological cures achieved with a double dose of benzathine penicillin G; lower numbers cured with a triple dose of benzathine penicillin G; similar numbers cured when treated with ceftriaxone, azithromycin or doxycycline; and slightly lower numbers cured with doxycycline and tetracycline together. Evidence also suggests that there may be little to no difference in the effects of different medicines in people living with HIV and those not living with HIV. Transmission to partners, HIV transmission and acquisition, and STI complications were not measured.

Few studies provided data for adverse events. Azithromycin may increase gastrointestinal side-effects and dizziness or headache (3–4 times greater than with benzathine penicillin G), but it may reduce rash (65% reduction), fever (50–65% reduction) and serious adverse events (30% reduction). Ceftriaxone may be less likely to cause diarrhoea and rash, but this evidence is uncertain. Data were not available on resistance to azithromycin for treating syphilis in specific settings,

and this will likely remain unknown in many places as the capacity to monitor AMR in *T. pallidum* is not available in many settings. Resistance to azithromycin for other conditions is spreading, and therefore the Guideline Development Group (GDG) was concerned about the risk of azithromycin resistance in *T. pallidum*.

There was some research evidence relating to overall acceptability of injections versus medicines taken orally in people with syphilis: approximately 10–20% of people refused injections. The GDG noted that in practice some health-care providers are averse to providing injections, and there are additional staff time and equipment costs with IM administration. The GDG raised concerns about the impending global shortage of benzathine penicillin; a shortage would reduce health equity and it would not be feasible to apply the treatment recommendation.

The GDG judged the benefits of treatment with benzathine penicillin G versus no treatment as large based on the historically successful treatment of syphilis over the past 70 years. It was also judged that the differences in benefits between medicines used for treatment are likely to be trivial. There were inconsistent results for greater benefit with higher doses of benzathine penicillin G. The differences in the undesirable anticipated effects (side-effects) were judged to be small. Because the benefits probably outweigh the harms, and because of the potential for resistance to azithromycin and greater cost, benzathine penicillin G was suggested. Benzathine penicillin G was also suggested over ceftriaxone and doxycycline due to the unknown side-effects and benefits of the latter two medicines, and the higher costs of ceftriaxone. The GDG also judged the administration of benzathine and procaine penicillins by injection as being acceptable to most people.

#### PREGNANT WOMEN RECOMMENDATION 3

In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.

*Strong recommendation, very low quality evidence*

#### RECOMMENDATION 4

In pregnant women with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once daily for 10 days.

*Conditional recommendation, very low quality evidence*

When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days or azithromycin 2 g once orally.

*Conditional recommendation, very low quality evidence*

**Remarks:** Although erythromycin and azithromycin treat the pregnant women, they do not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see recommendations 9 and 10 for congenital syphilis). Ceftriaxone is an expensive option and is injectable. Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, **stock-outs of benzathine penicillin for use in antenatal care should be avoided.**

#### SUMMARY OF THE EVIDENCE

The overall quality of the evidence for treatments used for pregnant women was very low. There were few studies (10 non-randomized studies) and very few pregnant women included in the studies. In most studies, the stage of syphilis (early or late) was unknown. The evidence in adults and adolescents, and the evidence from successful historical use of benzathine and procaine penicillins and erythromycin, was used to inform the judgements about the benefits of different medicines. The benefits were large for the use of benzathine penicillin compared to no treatment. The differences in medicines in terms of benefits and harms were trivial. Prevention of mother-to-child transmission (PMTCT) was a critical outcome. Penicillins cross the placental barrier, while azithromycin and erythromycin do not, meaning there is an increased chance of mother-to-child transmission of syphilis with the use of the latter medicines.

There was no evidence for adverse effects, transmission to partner, antimicrobial resistance (AMR), HIV transmission or acquisition, or STI complications. Research evidence for the other factors (acceptability, feasibility, equity and costs) was not specific to pregnant women. Therefore, evidence for non-pregnant adults was used to inform this recommendation.

Overall, the recommendations for non-pregnant women with early syphilis were used to inform the recommendations for pregnant women with early syphilis, with the exception of the use of doxycycline which cannot be used in pregnant women. Erythromycin was added as an alternative based on successful historical use.

## 4.2 LATE SYPHILIS (INFECTION OF MORE THAN TWO YEARS' DURATION WITHOUT EVIDENCE OF TREPONEMAL INFECTION)

### ADULTS AND ADOLESCENTS RECOMMENDATION 5

In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment.

*Strong recommendation, very low quality evidence*

**Remarks:** The interval between consecutive doses of benzathine penicillin should not exceed 14 days.

### RECOMMENDATION 6

In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once daily for 20 days.

*Conditional recommendation, very low quality evidence*

When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 30 days.

*Conditional recommendation, very low quality evidence*

**Remarks:** Doxycycline should not be used in pregnant women (see recommendations 7 and 8 for pregnant women).

### PREGNANT WOMEN RECOMMENDATION 7

In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment.

*Strong recommendation, very low quality evidence*

**Remarks:** The interval between consecutive doses of benzathine penicillin should not exceed 14 days.

### RECOMMENDATION 8

In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units intramuscularly once daily for 20 days.

*Conditional recommendation, very low quality evidence*

When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 30 days.

*Conditional recommendation, very low quality evidence*

**Remarks:** Although erythromycin treats the pregnant women, it does not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see recommendations 9 and 10 for congenital syphilis). Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, **stock-outs of benzathine penicillin for use in antenatal care should be avoided.**

### SUMMARY OF THE EVIDENCE

Overall, the quality of the evidence was very low. Most studies typically include people with early or late syphilis and don't distinguish between the stage of syphilis when reporting the results. However, one study included over 300 people diagnosed with late syphilis. It evaluated benzathine penicillin G 2.4 MU given once IM and azithromycin 2 g given once orally. Serological cure was low (33–39%); these doses are typically provided for early syphilis. Another study included 135 pregnant women treated for late syphilis. This study found that 99% of women with the double dose of benzathine penicillin G were cured. Historically, multiple doses of benzathine penicillin G (once a week for three weeks) or procaine penicillin 1.2 MU (once daily for 20 days) have been successful for serological and clinical cure of syphilis. For pregnant women, PMTCT is a critical outcome. Penicillins cross the placental barrier, while azithromycin and erythromycin do not, meaning that there is an increased chance of mother-to-child transmission of syphilis with the use of the latter medicines.

There has been some successful historical use of doxycycline 100 mg twice daily for 30 days, but not in pregnant women. There were no data for adverse events, transmission to partners, HIV transmission and acquisition, or STI complications. There are no reported data on resistance to azithromycin for treating syphilis in specific settings, and this will likely remain unknown in many places as the capacity to monitor AMR in *T. pallidum* is not available in many settings. Resistance to azithromycin for other conditions is spreading, and therefore the STI GDG was concerned about the risk of azithromycin resistance in *T. pallidum*.

Evidence used for making recommendations for treatment in early syphilis was used to inform this recommendation for late syphilis. There was some research evidence relating to overall acceptability of injections versus medicines taken orally in people with syphilis: approximately 10–20% of people refused injections. The GDG noted that in practice some health-care providers are averse to providing injections, and there are additional staff time and equipment costs with IM administration. The GDG raised concerns about the impending global shortage of benzathine penicillin; a shortage would reduce health equity and it would not be feasible to apply the treatment recommendation.

The GDG judged the benefits of treatment with benzathine penicillin G versus no treatment as large based on the historically successful treatment of syphilis over the past 70 years. It was also judged that the differences in benefits between medicines used for treatment are likely to be trivial. The differences in the undesirable anticipated effects (side-effects) were judged to be small. Because the benefits probably outweigh the harms, and because of the potential for resistance to azithromycin, greater cost and lack of historical data for azithromycin, benzathine penicillin G and procaine penicillin were suggested. The penicillins were suggested over doxycycline due to the lack of historical data in late syphilis and unknown side-effects and benefits of doxycycline. For pregnant women, the penicillins were also suggested over erythromycin since erythromycin does not cross the placental barrier. The GDG also judged the administration of benzathine and procaine penicillins by injection as being acceptable to most people.

## 4.3 CONGENITAL SYPHILIS

### INFANTS

#### RECOMMENDATION 9

In infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis (including treatment within 30 days of delivery) or syphilis that was treated with non-penicillin regimens, the WHO STI guideline suggests aqueous benzyl penicillin or procaine penicillin.

*Conditional recommendation, very low quality evidence*

Dosages:

- Aqueous benzyl penicillin 100 000–150 000 U/kg/day intravenously for 10–15 days
- Procaine penicillin 50 000 U/kg/day single dose intramuscularly for 10–15 days

**Remarks:** If an experienced venipuncturist is available, aqueous benzyl penicillin may be preferred instead of intramuscular injections of procaine penicillin.

#### RECOMMENDATION 10

In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, the WHO STI guideline suggests close monitoring of the infants.

*Conditional recommendation, very low quality evidence*

**Remarks:** The risk of transmission of syphilis to the fetus depends on a number of factors, including maternal titres from non-treponemal tests (e.g. RPR), timing of maternal treatment and stage of maternal infection, and therefore this recommendation is conditional.

If treatment is provided, benzathine penicillin G 50 000 U/kg/day single dose intramuscularly is an option.

## SUMMARY OF THE EVIDENCE

The overall quality of the evidence was very low. Nine non-randomized studies informed this recommendation, as well as historical use of the medicines to treat and prevent confirmed or suspected congenital syphilis. The sample sizes of most studies was small, and rates of follow-up of babies achieved after treatment were very low. When there was follow-up, it ranged from six months to one year. Treatments provided included aqueous benzyl penicillin, procaine penicillin and benzathine penicillin G; ceftriaxone was not assessed. In most studies of infants with confirmed congenital syphilis or infants whose mothers received inadequate or no treatment, treatment of infants resulted in 100% cures with no adverse effects. Aqueous benzyl penicillin or procaine penicillin were favoured over ceftriaxone due to little or no data, and known potential for side-effects and contraindications with the use of ceftriaxone to treat other conditions. There were some historical data (but no other data) indicating that benzathine penicillin G may have benefit and few adverse effects, but this is uncertain. There were no follow-up data for untreated infants who were clinically normal and born to mothers who had received adequate treatment. From global estimates, the risk of congenital syphilis for infants born alive to mothers with untreated syphilis is approximately 16 per 100 mothers. A systematic review found that when mothers are treated, the risk of congenital syphilis is 0.03 times the risk in infants born to untreated mothers; from this it can be roughly estimated that there would be 4.8 births with congenital syphilis per 1000 treated mothers. Only half of these infants (2.4 per 1000) would be expected to show signs or symptoms of congenital syphilis. Therefore, in 1000 treated mothers, there would be a risk of two to three infants born with congenital syphilis who are clinically normal.

There was little cost difference between aqueous benzyl penicillin or procaine penicillin, but ceftriaxone was more expensive. The GDG agreed that the medicines are available and thus availability would likely not have an impact on equity. However, for people who need to travel for treatment, health equity may be reduced. The GDG agreed that IM injections would be acceptable, given that finding a vein for intravenous (IV) administration is often very difficult for infants. However, if an experienced venupuncture is present and willing, benzyl penicillin could be administered IV.

Overall, historical data show benefits of treatment with aqueous benzyl penicillin and procaine penicillin with few to no adverse effects, and similar costs. There are little to no data for benzathine penicillin G, but there may be no adverse effects; there are also little to no data for ceftriaxone but adverse effects may occur and it is more expensive than the other medicines. A preference for IM injections or IV administration was not determined, but these options are available with either medication. Overall, the risk of congenital syphilis in infants born to mothers who have received adequate treatment was judged to be very low and therefore, monitoring of these infants is suggested over treatment.

# 05

## RESEARCH IMPLICATIONS

The Guideline Development Group (GDG) discussed the need to develop a new treatment. Ideally the new treatment should be a short course administered orally which can treat pregnant women with syphilis and cross the blood–brain and placental barriers to prevent transmission to the fetus. Cephalosporins could be potential options.

Trials investigating appropriate dosages and effectiveness of ceftriaxone use for early and late syphilis should be conducted. The trials should compare ceftriaxone with benzathine penicillin G and doxycycline. To what extent the medicines cross the blood–brain and placental barriers should also be investigated. More research should also be conducted into medicines that are taken orally for a few days, such as cephalosporins. Since benzathine penicillin G and other penicillins require injection by health workers, it was suggested that the safety of self-injection be investigated.

There was little data for ceftriaxone use in infants with confirmed congenital syphilis and therefore research is needed, in particular comparing ceftriaxone to procaine penicillin.

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## ANNEX A: STI GUIDELINE DEVELOPMENT TEAMS

### WHO STI STEERING COMMITTEE

WHO regional STI focal points		Region
1.	<b>Massimo Ghidinelli</b>	Region of the Americas (AMR) Washington, DC – United States of America (USA)
2.	<b>Lali Khotenashvili</b>	European Region (EUR) Copenhagen – Denmark
3.	<b>Ying-Ru Lo</b>	Western Pacific Region (WPR) Manila – Philippines
4.	<b>Frank Lule</b>	African Region (AFR) Brazzaville – Congo
5.	<b>Razia Pendse and Ornella Lincetto</b>	South-East Asia Region (SEAR) New Delhi – India WHO Country Representative, Bhutan
6.	<b>Hamida Khattabi and Gabriela Reidner</b>	Eastern Mediterranean Region (EMR) Cairo – Egypt
WHO headquarters		Department and Team
7.	<b>Moazzam Ali</b>	Department of Reproductive Health and Research Human Reproduction Team
8.	<b>Avni Amin</b>	Department of Reproductive Health and Research Adolescents and at-Risk Populations
9.	<b>Rachel Baggaley</b>	Department of HIV/AIDS Key Populations and Innovative Prevention
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AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region;  
 EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region

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## ANNEX B: DETAILED METHODS FOR GUIDELINES DEVELOPMENT

### QUESTIONS AND OUTCOMES

To determine which recommendations to update, in December 2013 the World Health Organization (WHO) Department of Reproductive Health and Research reviewed current recommendations of key international guidelines:

- Sexually transmitted diseases treatment guidelines, 2010, Department of Health and Human Services, United States Centers for Disease Control and Prevention (CDC)<sup>4</sup>;
- United Kingdom national guidelines for the management of sexually transmitted infections, British Association for Sexual Health and HIV (BASHH), 2006–2011;<sup>5</sup>
- Canadian guidelines on sexually transmitted infections, Public Health Agency of Canada, 2013–2014;<sup>6</sup>
- European sexually transmitted infections guidelines, International Union of Sexually Transmitted Infections (IUSTI);<sup>7</sup>
- National management guidelines for sexually transmissible infections, Sexual Health Society of Victoria, Australia, 2008;<sup>8</sup>
- National guideline for the management and control of sexually transmitted infections (STIs), National Department of Health, South Africa, 2009;<sup>9</sup> and
- National guidelines on prevention, management and control of reproductive tract infections including sexually transmitted infections, Ministry of Health and Family Welfare, Government of India, August 2007.<sup>10</sup>

Based on the review, four proposed categories of sexually transmitted infection (STI) conditions were prioritized:

- a. STI conditions included in the 2003 WHO STI guidelines<sup>11</sup> that were selected by the GDG to be reviewed and updated in the new WHO STI guidelines. These are important and common conditions.
- b. STI conditions not included in the 2003 WHO STI guidelines that were selected by the GDG to be reviewed and added in the new WHO STI guidelines. These are important and common conditions.
- c. STI conditions included in the 2003 WHO STI guidelines that were not updated but were selected by the GDG to be included in the new WHO STI guidelines. These STI conditions are rare and diagnosis is not often made in the majority of settings, or it is unlikely that there is new information available as a basis for making any changes to the 2003 WHO STI recommendations.
- d. STI conditions not included in the 2003 WHO STI guidelines that are part of other national guidelines, but were not selected by the GDG to be included in the new WHO STI guidelines. These conditions are rare and difficult to diagnose in the majority of settings, or it is unlikely that new research or information has become available; there are existing recommendations for these conditions that can be applied in other settings (e.g. reference hospitals that manage complicated conditions).

<sup>4</sup> Available at: <http://www.cdc.gov/std/treatment/2010/std-treatment-2010-rr5912.pdf>

<sup>5</sup> Available at: <http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx?hkey=072c83ed-0e9b-44b2-a989-7c84e4fb9de>

<sup>6</sup> Available at: <http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-lcdcts/index-eng.php>

<sup>7</sup> Available at: <http://www.iusti.org/regions/europe/euroguidelines.htm>

<sup>8</sup> Melbourne Sexual Health Centre Treatment Guidelines, available at: <http://mshc.org.au/HealthProfessional/MSHTreatmentGuidelines/tabid/116/Default.aspx>

<sup>9</sup> DA Lewis, E Maruma. Revision of the national guideline for first-line comprehensive management and control of sexually transmitted infections: what's new and why? *South Afr J Epidemiol Infect.* 2009;24(2):6–9 (<http://apps.who.int/medicinedocs/documents/s18369en/s18369en.pdf>).

<sup>10</sup> Available at: [http://www.ilo.org/wcmsp5/groups/public/---ed\\_protect/---protrav/---ilo\\_aids/documents/legaldocument/wcms\\_117313.pdf](http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/legaldocument/wcms_117313.pdf)

<sup>11</sup> Guidelines for the management of sexually transmitted infections. Geneva: World Health Organization; 2003 (<http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf>, accessed 30 May 2016).

A meeting was held in December 2013, at which the Guideline Development Group (GDG) discussed and decided on the initial list of population, intervention, comparator and outcome (PICO) questions identified by WHO. After the meeting, surveys pertaining to each of the four STI topic areas (i.e. gonorrhoea, chlamydia, syphilis and genital herpes simplex virus) were administered among subgroups of the GDG members with expertise relating to the relevant STIs. The goal of the surveys was to rank the population, interventions and outcomes for each specific STI condition by importance. The surveys required the members of the STI subgroups to rank the population, interventions and outcomes on a scale of 1 to 9, from lowest to highest priority.

Four different priority STI surveys were conducted, and each survey attained a 90–100% response rate from the STI subgroup members. The survey results for priority populations, interventions and outcomes were analysed. Populations, interventions and outcomes with an average rating of 7 to 9 were considered “critical”; those with an average rating of 4 to 6 were considered “important”; and those with an average rating of 1 to 3 were considered “not important” and were thus not covered in the guidelines. Some questions that scored less than 7 were kept for consistency.

The number of comparisons in each question was also reduced; only “critical” interventions were compared with each other and with important interventions. Thus, “important” interventions were not compared to each other.

A revised list of questions was then compiled and all members of the full STI GDG were requested to review the priority questions. The priority questions were then revised based on this feedback.

Nine questions were identified for the update of the syphilis guidelines and used to inform the recommendations. Each question is framed using the PICO format (population, intervention, comparison, and outcomes).

## PRIORITY QUESTIONS AND OUTCOMES FOR *TREPONEMA PALLIDUM* (SYPHILIS)

### EARLY SYPHILIS: ADULTS AND ADOLESCENTS (RECOMMENDATIONS 1 AND 2)

**Question 1:** Should benzathine penicillin G 2.4 million units (MU) x 1 compared with other treatments be used for treating adults and adolescents, including people living with HIV, with early syphilis?

**Early syphilis (primary, secondary or latent < 2 years) in adults and adolescents and people living with HIV**

Population	Intervention	Comparator	Outcome
Adults and adolescents and people living with HIV with early syphilis (primary, secondary or latent < 2 years)	Benzathine PCN 2.4 MU x 1	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 Benzathine PCN 2.4 MU x 3 doses Benzathine PCN 2.4 MU x 2 doses Doxycycline 100 mg po bid x 14 days Erythromycin 500 mg po qid x 14 days	<b>Critical:</b> Serological response, clinical cure  <b>Important:</b> Transmission to partner, antimicrobial resistance, compliance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications

bid: twice daily; IM: intramuscular; MU: million units; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

**Question 2:** Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating adults and adolescents, including people living with HIV, with early syphilis with penicillin allergy?

**Early syphilis (primary, secondary or latent < 2 years) in patients with penicillin allergy**

Population	Intervention	Comparator	Outcome
Patients with penicillin allergy with early syphilis (primary, secondary or latent < 2 years)	PCN desensitization and PCN	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 Doxycycline 100 mg po bid x 14 days Erythromycin 500 mg po qid x 14 days	<b>Critical:</b> Serological response, clinical cure, allergic reaction/anaphylactic shock <b>Important:</b> Transmission to partner, antimicrobial resistance, compliance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications

bid: twice daily; IM: intramuscular; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

**EARLY SYPHILIS: PREGNANT WOMEN (RECOMMENDATIONS 3 AND 4)**

**Question 3:** Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis?

**Early syphilis (primary, secondary or latent < 2 years) in pregnant women**

Population	Intervention	Comparator	Outcome
Pregnant women with early syphilis (primary, secondary or latent < 2 years)	Benzathine PCN 2.4 MU x 1	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 dose Benzathine PCN 2.4 MU x 3 doses Benzathine PCN 2.4 MU x 2 doses Erythromycin 500 mg po qid x 14 days	<b>Critical:</b> Mother-to-child transmission, serological response, low birth weight/preterm, stillbirth/neonatal death, clinical cure, congenital deformities, side-effects (including allergy, toxicity) <b>Important:</b> Compliance, antimicrobial resistance, STI complications, transmission to partner, HIV transmission or acquisition

IM: intramuscular; MU: million units; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

**Question 4:** Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis with penicillin allergy?

**Early syphilis (primary, secondary or latent < 2 years) in pregnant women with penicillin allergy**

Population	Intervention	Comparator	Outcome
Pregnant women with penicillin allergy with early syphilis (primary, secondary or latent < 2 years)	PCN desensitization and PCN	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 Erythromycin 500 mg po qid x 14 days	<b>Critical:</b> Mother-to-child transmission, serological response, low birth weight/preterm, stillbirth/neonatal death, clinical cure, congenital deformities, side-effects (Including allergy, toxicity), anaphylaxis <b>Important:</b> Compliance, antimicrobial resistance, STI complications, transmission to partner, HIV transmission or acquisition

IM: intramuscular; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

**LATE SYPHILIS: ADULTS AND ADOLESCENTS (RECOMMENDATIONS 5 AND 6)**

**Question 5:** Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used in adults and adolescents, including people living with HIV, with late syphilis?

**Late syphilis (latent syphilis or syphilis of unknown duration) in adults and adolescents and people living with HIV**

Population	Intervention	Comparator	Outcome
Adults and adolescents and people living with HIV with latent syphilis > 2 years or syphilis of unknown duration	Benzathine PCN 2.4 MU IM 3 doses (1 dose per week x 3 weeks)	Azithromycin Ceftriaxone 1 g IM or IV qd x 10 days Benzathine PCN 2.4 MU x 1, 2 doses over 2 weeks Doxycycline 100 mg po bid x 30 days Erythromycin 500 mg po qid x 30 days	<b>Critical:</b> Serological response, compliance <b>Important:</b> Transmission to partner, antimicrobial resistance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications

bid: twice daily; IM: intramuscular; IV: intravenous; MU: million units; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

### LATE SYPHILIS: PREGNANT WOMEN (RECOMMENDATIONS 7 AND 8)

**Question 6:** Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used for treating pregnant women with late syphilis?

#### Late syphilis (latent syphilis or syphilis of unknown duration) in pregnant women

Population	Intervention	Comparator	Outcome
Pregnant women with latent syphilis > 2 years or syphilis of unknown duration	Benzathine PCN 2.4 MU IM 3 doses (1 dose per week x 3 weeks)	Azithromycin Ceftriaxone 1 g IM or IV qd x 10 days Benzathine PCN 2.4 MU x 1, 2 doses over 2 weeks Erythromycin 500 mg po qid x 30 days	<b>Critical:</b> Mother-to-child transmission, serological response, low birth weight/preterm, stillbirth/neonatal death, congenital deformities, compliance  <b>Important:</b> Antimicrobial resistance, STI complications, transmission to partner, HIV transmission or acquisition, side-effects (including allergy, toxicity)

IM: intramuscular; IV: intravenous; MU: million units; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

### CONGENITAL SYPHILIS: INFANTS (RECOMMENDATIONS 9 AND 10)

**Question 7:** In infants with congenital syphilis, or in infants whose mothers had untreated syphilis, inadequately treated syphilis or adequately treated syphilis, what are the treatment options?

#### Multiple scenarios of proven or possible infection:

##### Scenario 1: Infants with congenital syphilis

Population	Intervention	Comparator	Outcome
Infants with congenital syphilis	Benzyl penicillin 100 000–150 000 U/kg/day x 10–15 days  Procaine penicillin 50 000 U/kg/day x 10–15 days	Ceftriaxone:  • Infants < 30 days: Ceftriaxone 75 mg/kg BW IM/IV single dose x 10–14 days • Infants ≥ 30 days: Ceftriaxone 100 mg/kg BW IM/IV single dose x 10–14 days	<b>Critical:</b> Clinical cure, serologic response, congenital syphilis manifestation

BW: body weight; IM: intramuscular; IV: intravenous

**Question 8:** In infants who are clinically normal but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens, what are the treatment options?

**Scenario 2: Infants who are clinically normal but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens**

Population	Intervention	Comparator	Outcome
Infants clinically normal, but mother with syphilis not treated, inadequately treated or treated with non-penicillin	Benzyl penicillin 100 000–150 000 U/kg/day x 10 days to 15 days  Procaine penicillin 50 000 U/kg/day x 10–15 days	Benzathine penicillin 50 000 U/kg IM single dose  Ceftriaxone: <ul style="list-style-type: none"><li>• Infants &lt; 30 days: Ceftriaxone 75 mg/kg BW IM/IV single dose x 10–14 days</li><li>• Infants ≥ 30 days: Ceftriaxone 100 mg/kg BW IM/IV single dose x 10–14 days</li></ul> No treatment	<b>Critical:</b> Clinical cure, serologic response, congenital syphilis manifestation

BW: body weight; IM: intramuscular; IV: intravenous

**Question 9:** In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, what is the recommended course of action?

**Scenario 3: Infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection**

Population	Intervention	Comparator	Outcome
Infants clinically normal, but mother treated, no signs of reinfection	Benzathine penicillin 50 000 U/kg IM single dose	No treatment  Ceftriaxone: <ul style="list-style-type: none"><li>• Infants &lt; 30 days: Ceftriaxone 75 mg/kg BW IM/IV single dose x 1 day</li><li>• Infants ≥ 30 days: Ceftriaxone 100 mg/kg BW IM/IV single dose x 1 day</li></ul>	<b>Critical:</b> Clinical cure, serologic response, congenital syphilis manifestation

BW: body weight; IM: intramuscular; IV: intravenous

## REVIEW OF THE EVIDENCE

### SEARCH FOR EVIDENCE FOR EFFECTS OF INTERVENTIONS

To avoid duplication of reviews that have been previously published, evidence was searched using a hierarchical approach. The team first searched for synthesized evidence then searched the primary studies for all the factors needed to complete the evidence-to-decision framework for each question (i.e. benefits and harms, patient values, acceptability, feasibility, equity and costs).

The hierarchical approach consisted of identifying pre-existing synthesized evidence, including from previously published guidelines that included systematic reviews of the literature. When synthesized evidence about benefits and harms for an intervention was not available or the synthesized evidence was not up to date, a new systematic review of randomized controlled trials (RCTs) and non-randomized studies was conducted.

The search strategies were developed by an information specialist trained in systematic reviews. The strategies included the use of keywords from the controlled vocabulary of the database and text words based on the PICO questions. There were no restrictions based on language, publication status or study design. RCTs were included for critical and important outcomes, and non-randomized studies for critical outcomes when no evidence was available from RCTs. Additional strategies included contacting Cochrane review groups and authors of study protocols.

The Cochrane Library suite of databases (Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment [HTA] database and the American College of Physicians [ACP] Journal Club) was searched for published systematic reviews and protocols up to January 2014.

#### Search strategy:

1. treponema.mp.
2. pallidum.mp.
3. syphilis.mp.
4. chancre\*.mp.
5. or/1-4

Primary studies were searched for in the Cochrane Central Register of Controlled Trials (CENTRAL) (up to March 2015), MEDLINE and Embase databases (up to 26 February 2015) and LILACS (up to 19 April 2015).

The strategies included searching for subject headings and text words related to syphilis and specific interventions (e.g. medication names and classes). Additional strategies included checking reference lists and consulting with the GDG for any missed articles.

### SCREENING STUDIES, DATA EXTRACTION AND ANALYSIS

Two researchers independently screened titles and abstracts of systematic reviews identified through database searching to determine studies eligible for inclusion in the analysis. Disagreements were resolved by discussing study inclusion with a third member of the research team. Data were extracted using a pilot-tested form for patient characteristics (including the subgroups identified by the GDG), diagnosis, treatment (dose, schedule, etc.), setting, follow-up and outcomes. Two investigators independently abstracted data. Risk of bias of each study was also assessed using risk of bias tools appropriate for RCTs ([http://handbook.cochrane.org/chapter\\_8/8\\_assessing\\_risk\\_of\\_bias\\_in\\_included\\_studies.htm](http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm)) and using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I; previously called ACROBAT) tool to assess non-randomized studies ([www.riskofbias.info](http://www.riskofbias.info)).

To measure the treatment effect, the data were analysed using RevMan 5.2.<sup>12</sup>

For dichotomous outcomes, we calculated relative risks with 95% confidence intervals (e.g. risk ratios and odds ratios) by pooling results from RCTs and pooling results from non-randomized studies using the random effects model. Moderate to high heterogeneity ( $I^2 > 50\%$ ) was explored. Effects were converted to absolute effects using the calculated relative effect and a representative baseline risk (agreed upon by the GDG). When non-randomized studies with one group were included, a pooled proportion of an event (and confidence intervals) were calculated across the studies using the generic inverse variance. For continuous outcomes, a mean difference or a standardized mean difference (when studies used different scales to measure an outcome) was calculated. When possible, the forest plots of the meta-analyses were made available to the GDG.

When data could not be pooled across studies, narrative synthesis methods were used (see <http://methods.cochrane.org/files/Mckenzie.pdf>). Results were presented in tables (e.g. median effects with interquartile ranges), or were narratively described by direction of the effect or by statistical significance as reported in the primary study.

## PATIENT VALUES AND PREFERENCES, ACCEPTABILITY, EQUITY AND FEASIBILITY

Studies on patient values and preferences, acceptability, equity and feasibility were searched for and screened using two methods. First, while screening studies for the effects of treatments and costs, two investigators identified studies of potential relevance in these areas. Secondly, a separate search was conducted in MEDLINE, Embase and PsycINFO from January 2000 to July 2015. Text words and keywords for the different STIs were used in combination with words such as "preference", "adherence", "satisfaction", "attitudes", "health utilities" and "value", "equity" and "feasibility". The results included 2563 unique references. Two investigators screened the studies, and 162 studies were identified for full text retrieval. Any study design was included that addressed equity or feasibility. In addition, when adherence was measured in RCTs or non-randomized studies, the data were collected, synthesized and presented in the evidence profiles for each PICO question.

The following study designs were included:

a. Patient utilities and health status values studies:

These studies examine how patients value alternative health states and their experiences with treatment. The measurement techniques used can include: standard gamble, time trade-off, visual analogue scale, or mapping results based on generic surveys (EuroQol five dimensions health questionnaire [EQ-5D] or the 36-Item Short Form Health Survey [SF-36]) or specific measurement (e.g. St George Respiratory Questionnaire) of health-related quality of life.

b. Studies of patients' direct choices when presented with decision aids: These studies examine the choices patients make when presented with decision aids for management options (i.e. probabilistic trade-off techniques).

c. Studies on non-utility measurement of health states: These studies quantitatively examine patients' views, attitudes, satisfaction or preferences through questionnaires or scales; these are neither utility studies nor studies of patients' responses to decision aids. Patients are asked about how desirable or aversive a particular outcome is for them. This category includes some studies that use questionnaires or scales.

d. Qualitative studies: These studies explore patients' views, attitudes, satisfactions or preferences related to different treatment options based on qualitative research methods including focus group discussions, interviews, etc.

From the search, we included 17 studies reporting information relating to different STIs. In many instances, data for all infections informed the evidence for syphilis specifically.

## RESOURCES

We searched the published literature for evidence on use of resources and obtained data on direct costs of medicines.

Based on the list of possible treatments identified by the GDG, an estimate of the cost associated with each alternative was calculated. This costing estimate refers only to the actual market price of the medication and does not include the costs of other resources that could be involved, such as syringes, injection time or needle disposal.

Data were presented in a table and included: treatment, dose per day, treatment duration, days, medicine cost per dose, medicine cost per full course of treatment, and 25% of procurement costs (as defined in the 2014 Management Sciences for Health (MSH) International drug price indicator guide)<sup>13</sup>. A final price for a full course of treatment for each medicine by dosage was calculated as the number of doses per day, multiplied by the number of days of the treatment, plus 25% of the procurement costs for the medicines used. The unit price of the medicine was obtained from the median prices provided in the 2014 MSH International drug price indicator guide and information available on the Internet. In order to determine a precise and reliable estimate, the price per unit (all expressed in US dollars) was provided only when the information available matched the dosage of interest (grams per pill or 1000 units per vial). No calculations were made based on assumptions about the cost per unit of hypothetical packaging not listed in the directory.

The major medical databases were also searched (MEDLINE, Embase and the Cochrane Library for Economic Evaluation and Technology Assessment reports) from January 2005 to July 2015. In addition, while screening studies for the effects of treatments, two investigators also identified studies of potential relevance for costs. No studies were identified for resource use relating to treatment of syphilis.

<sup>13</sup> International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Sciences for Health; 2015 ([http://erc.msh.org/dmpguide/pdf/DrugPriceGuide\\_2014.pdf](http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2014.pdf), accessed 6 June 2016).

## APPLYING THE GRADE APPROACH TO MAKING THE RECOMMENDATIONS

### EVIDENCE PROFILES

An evidence profile was made for each PICO question using the GRADEpro software ([www.gradepro.org](http://www.gradepro.org)). Each profile included the critical and important outcomes, the relative and absolute effects, and the quality of evidence according to the GRADE domains (see the GRADE handbook)<sup>14</sup>. Briefly, the GRADE approach assesses the quality of evidence for treatment interventions using well-established criteria for the design, risk of bias, inconsistency, indirectness, imprecision, effect size, dose-response curve and other considerations that may affect the quality of the evidence. Two investigators used the GRADE approach to assess the quality and level of certainty of the evidence. The evidence profiles for each recommendation are available in Web annex D.

### EVIDENCE-TO-DECISION FRAMEWORKS

Evidence-to-decision frameworks were also developed using GRADEpro software ([www.gradepro.org](http://www.gradepro.org)). Evidence-to-decision frameworks present the desirable and undesirable effects of the interventions, the value of the outcomes, the costs and resource use, the acceptability of the interventions to all stakeholders, the impact on health equity, and the feasibility of implementation (i.e. the GRADE criteria for making decisions). The evidence-to-decision frameworks are based on a population perspective for these recommendations. All GRADE criteria were considered from this perspective.

### MAKING THE RECOMMENDATIONS

In October 2015, the GDG met to make the recommendations. This meeting was facilitated by two co-chairs – one with expertise in GRADE and the other with clinical expertise of syphilis. During the meeting, the evidence profiles and evidence-to-decision frameworks were presented by the methodologists. The GDG discussed each GRADE criterion and judged which intervention was favoured. Then a final decision and guideline recommendation was developed. The goal was to arrive at agreement across all members of the GDG and this was facilitated by the chairpersons through discussion. When there was disagreement for a criterion, it was noted in the evidence-to-decision framework for the relevant judgement. If there was disagreement for any of the final recommendations, the plan was for the GDG to vote and the numbers to be recorded. Because there was no disagreement for any of the final recommendations, however, votes were not taken or reported in these guidelines.

The GDG made a strong or conditional recommendation for or against each intervention and described special circumstances in the remarks. Research implications were also developed and presented, based on the gaps identified in the evidence. Following the meeting, the recommendations were finalized via teleconference, and final approval was obtained from the GDG members electronically. All decisions and discussions from the GDG for each recommendation are available in the evidence-to-decision frameworks in Web annex D.

<sup>14</sup> Schünemann H, Brožek J, Guyatt G, Oxman A, editors. GRADE handbook. Hamilton, Ontario: McMaster University and Evidence Prime Inc.; 2013 ([http://gdt.guidelinedevelopment.org/central\\_prod/\\_design/client/handbook/handbook.html](http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html), accessed 31 May 2016).

## ANNEX C: LISTS OF REFERENCES FOR REVIEWED EVIDENCE

### RECOMMENDATION 1 AND 2

**Question 1: Should benzathine penicillin G 2.4 million units (MU) x 1 compared with other treatments be used for treating adults and adolescents including people living with HIV with early syphilis?**

**Question 2: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating adults and adolescents, including people living with HIV, with early syphilis with penicillin allergy?**

#### Systematic reviews

1. Bai ZG, Wang B, Yang K, Tian JH, Ma B, Liu Y, Jiang L, Gai QY, He X, Li Y. Azithromycin versus penicillin G benzathine for early syphilis. Cochrane Database Syst Rev. 2012;(6):CD007270.
2. Blank LJ, Rompalo AM, Erbelding EJ, Zenilman JM, Ghanem KG. Treatment of syphilis in HIV-infected subjects: a systematic review of the literature. Sex Transm Infect. 2011;87:9e16.
3. Blencowe H, Cousens S, Kamb M, Berman S, Lawn JE. Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. BMC Public Health. 2011;11(Suppl 3):S9.
4. Clement ME, Lance NO, Hicks CB. Treatment of syphilis: a systematic review. JAMA. 2014;312(18):1905-17.
5. Galvao TF, Silva MT, Serruya SJ, Newman LM, Klausner JD, Pereira MG, Fescina R. Safety of benzathine penicillin for preventing congenital syphilis: a systematic review. PLoS One. 2013;8(2):e56463. doi:10.1371/journal.pone.0056463.
6. Agmon-Levin N, Elbirt D, Asher I, Gradstein S, Werner B, Stoeger Z. Syphilis and HIV co-infection in an Israeli HIV clinic: incidence and outcome. Int J STD AIDS. 2010;21(4):249-52.
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9. Ghanem KG, Erbelding EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. Clinical Infect Dis. 2006;42(6):e45-9. doi:10.1086/500406.
10. González-López JJ, Fernández Guerrero ML, Luján R, Fernandez Tostado S, de Górgolas M, Requena L. Factors determining serologic response to treatment in patients with syphilis. Clin Infect Dis. 2009;49(10):1505-11. doi:10.1086/644618.
11. Hook IEW, Martin DH, Stephens J, Smith BS, Smith K. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. Sex Transm Dis. 2002;29(8):486-90.
12. Hook IEW, Behets F, Van Damme K, Ravelomanana N, Leone P, Sena AC et al. A Phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis. 2010;201(11):1729-35.
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16. Kiddugavu Mg, Kiwanuka N, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F et al.; Rakai Study Group.. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. Sex Transm Dis. 2005;32(1):1-6.
17. Li J, Zheng HY. Early syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. J Infect Dev Ctries. 2014;8(2):228-32. doi:10.3855/jidc.3013.
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27. Tong ML, Lin LR, Liu GL, Zhang HL, Zeng YL, Zheng WH et al. Factors associated with serological cure and the serofast state of HIV-negative patients with primary, secondary, latent, and tertiary syphilis. PLoS One. 2013;8(7):e70102.

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7. Van Dellen RG. Skin testing for penicillin allergy. *J Allergy Clin Immunol.* 1981;68:169-70.

## RECOMMENDATION 3 AND 4

**Question 3: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis?**

**Question 4: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis with penicillin allergy?**

### Systematic review

1. Blencowe H, Cousens S, Kamb M, Berman S, Lawn JE. Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. *BMC Public Health.* 2011;11(Suppl 3):S9.

### Included studies

1. Alexander JM, Sheffield JS, Sanchez PJ, Mayfield J, Wendel Jr GD. Efficacy of treatment for syphilis in pregnancy. *Obstet Gynecol.* 1999;93(1):5-8.
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4. Klein VR, Cox SM, Mitchell MD, Wendel GD Jr. The Jarisch-Herxheimer reaction complicating syphilitotherapy in pregnancy. *Obstet Gynecol.* 1990;75(3 Pt 1):375-80.
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1. Chauhan M, Serisha B, Sankar KN, Pattman RS, Schmid ML. Audit of the use of benzathine penicillin, post-treatment syphilis serology and partner notification of patients with early infectious syphilis. *Int J STD AIDS.* 2006;17(3):200-2
2. Crowe G, Theodore C, Forster GE, Goh BT. Acceptability and compliance with daily injections of procaine penicillin in the outpatient treatment of syphilis-treponemal infection. *Sex Transm Dis.* 1997;24(3):127-30.
3. Kingston MA, Higgins SP. Audit of the management of early syphilis at North Manchester General Hospital. *Int J STD AIDS.* 2004;15(5):352-4.
4. Owusu-Edusei K, Gift TL, Ballard RC. Cost-effectiveness of a dual non-treponemal/treponemal syphilis point-of-care test to prevent adverse pregnancy outcomes in sub-Saharan Africa (Provisional abstract). *Sex Transm Dis.* 2011;38:997-1003.
5. Tayal S, Ahmed MS, Hanif U. Audit of early syphilis: Teesside experience 2005-2007. *Int J STD AIDS.* 2009;20(9):647-9.

### Penicillin allergy

#### Systematic review

1. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA.* 2001;285(19):2498-505.

#### Included studies

1. You might be allergic to penicillin. Then again, you might not. In: ACAAI.org [website]. Arlington Heights (IL): American College of Allergy, Asthma and Immunology (ACAAI); 2014 (<http://acai.org/news/you-might-be-allergic-penicillin-then-again-you-might-not>, accessed 30 June 2016).
2. Co Minh HB, Bousquet PJ, Fontaine C, Kvedariene V, Demoly P. Systemic reactions during skin tests with beta-lactams: a risk factor analysis. *J Allergy Clin Immunol.* 2006;117:466-8.
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4. Nolan RC, Puy R, Deckert K, O'Hehir RE, Douglass JA. Experience with a new commercial skin testing kit to identify IgE-mediated penicillin allergy. *Intern Med J.* 2008;38:357-61.
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1. Chauhan M, Serisha B, Sankar KN, Pattman RS, Schmid ML. Audit of the use of benzathine penicillin, post-treatment syphilis serology and partner notification of patients with early infectious syphilis. *Int J STD AIDS.* 2006;17(3):200-2.
2. Crowe G, Theodore C, Forster GE, Goh BT. Acceptability and compliance with daily injections of procaine penicillin in the outpatient treatment of syphilis-treponemal infection. *Sex Transm Dis.* 1997;24(3):127-30.
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4. Owusu-Edusei K, Gift TL, Ballard RC. Cost-effectiveness of a dual non-treponemal/treponemal syphilis point-of-care test to prevent adverse pregnancy outcomes in sub-Saharan Africa (Provisional abstract). *Sex Transm Dis.* 2011;38:997-1003.
5. Tayal S, Ahmed MS, Hanif U. Audit of early syphilis: Teesside experience 2005–2007. *Int J STD and AIDS.* 2009;20(9):647-9.

## RECOMMENDATION 5 AND 6

**Question 5: Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used in adults and adolescents including people living with HIV with late syphilis?**

**Systematic review**

1. Bai ZG, Wang B, Yang K, Tian JH, Ma B, Liu Y et al. Azithromycin versus penicillin G benzathine for early syphilis. *Cochrane Database Syst Rev.* 2012;(6):CD007270.
2. Blank LJ, Rompalo AM, Erbelding EJ, Zenilman JM, Ghanem KG. Treatment of syphilis in HIV-infected subjects: a systematic review of the literature. *Sex Transm Infect.* 2011;87:9e16.
3. Blencowe H, Cousens S, Kamb M, Berman S, Lawn JE. Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. *BMC Public Health.* 2011;11(Suppl 3):S9.
4. Clement ME, Lance NO, Hicks CB. Treatment of syphilis: a systematic review. *JAMA.* 2014;312(18):1905-17.
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**Included studies**

1. Kiddugavu MG. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. *Sex Transm Dis.* 2005;32(1):1-6.

**Patient values and preferences, acceptability and cost: specific to syphilis infections**

1. Chauhan M, Serisha B, Sankar KN, Pattman RS, Schmid ML. Audit of the use of benzathine penicillin, post-treatment syphilis serology and partner notification of patients with early infectious syphilis. *Int J STD AIDS.* 2006;17(3):200-2
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5. Tayal S, Ahmed MS, Hanif U. Audit of early syphilis: Teesside experience 2005–2007. *Int J STD AIDS.* 2009;20(9):647-9.

## RECOMMENDATION 7 AND 8

**Question 6: Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used for treating pregnant women with late syphilis?**

**Systematic review**

1. Bai ZG, Wang B, Yang K, Tian JH, Ma B, Liu Y et al. Azithromycin versus penicillin G benzathine for early syphilis. *Cochrane Database Syst Rev.* 2012;(6):CD007270.
2. Blank LJ, Rompalo AM, Erbelding EJ, Zenilman JM, Ghanem KG. Treatment of syphilis in HIV-infected subjects: a systematic review of the literature. *Sex Transm Infect.* 2011;87:9e16.
3. Blencowe H, Cousens S, Kamb M, Berman S, Lawn JE. Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. *BMC Public Health.* 2011;11(Suppl 3):S9.
4. Clement ME, Lance NO, Hicks CB. Treatment of syphilis: a systematic review. *JAMA.* 2014;312(18):1905-17.
5. Galvao TF, Silva MT, Serruya SJ, Newman LM, Klausner JD, Pereira MG, Fescina R. Safety of benzathine penicillin for preventing congenital syphilis: a systematic review. *PLoS One.* 2012;8(2):e56463. doi:10.1371/journal.pone.0056463.

**Included studies**

1. Alexander JM, Sheffield JS, Sanchez PJ, Mayfield J, Wendel Jr GD. Efficacy of treatment for syphilis in pregnancy. *Obstet Gynecol.* 1999;93(1):5-8.

**Patient values and preferences, acceptability and cost: specific to syphilis infections**

1. Chauhan M, Serisha B, Sankar KN, Pattman RS, Schmid ML. Audit of the use of benzathine penicillin, post-treatment syphilis serology and partner notification of patients with early infectious syphilis. *Int J STD AIDS.* 2006;17(3):200-2.
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3. Kingston MA, Higgins SP. Audit of the management of early syphilis at North Manchester General Hospital. *Int J STD AIDS.* 2004;15(5):352-4.
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## RECOMMENDATION 9

**Question 7: In infants with congenital syphilis or in infants whose mothers had untreated syphilis, inadequately treated syphilis or adequately treated syphilis, what are the treatment options?**

**Question 8: In infants who are clinically normal but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens, what are the treatment options?**

## RECOMMENDATION 10

**Question 9: In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, what is the recommended course of action?**

### Systematic review

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**Patient values and preferences, acceptability and cost: specific to syphilis infections**

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