Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV

Developed by the National Institutes of Health, the HIV Medicine Association, and the Infectious Diseases Society of America Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Opportunistic Infection Guidelines:

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It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the Clinicalinfo website (https://clinicalinfo.hiv.gov/).

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What's New in the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV*

The *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV* document is published in an electronic format and updated as relevant changes in prevention and treatment recommendations occur.

All changes are developed by the subject-matter groups listed in the document. (Changes in group composition also are posted promptly.) These changes are reviewed by the editors and relevant outside reviewers before the document is altered. Major revisions within the last 6 months are as follows:

December 16, 2024

Hepatitis B Virus

- Recommended Heplisav-B as the preferred vaccine for all people with HIV, including those who are vaccine naive or prior vaccine nonresponders.

- Included a new section on considerations of nucleos(t)ide-sparing regimens in people with past hepatitis B virus (HBV), chronic HBV, and isolated hepatitis B core antibody positivity.

- Changed the consideration for pegylated interferon to an alternative treatment used only in rare cases.

- Removed PreHevbrio since it no longer will be available in the United States.

November 12, 2024

Immunizations

- Updated COVID-19 and influenza recommendations with new information on current vaccine formulations and data supporting their use.

- Provided new recommendations for the use of respiratory syncytial virus vaccines, including data supporting their use.

- Updated HepBCpG (Heplisav-B) to the preferred hepatitis B vaccine for people with HIV.

- Added pentavalent meningococcal conjugate vaccine (MenABCWY) recommendations as an alternative to separate administration of quadrivalent meningococcal vaccine and meningococcal group B vaccine.

October 29, 2024

Coccidioidomycosis

- Added isavuconazole sulfate as an alternative treatment for mild-to-moderate pulmonary infections.

- Updated the recommended fluconazole dosing for treatment of coccidioidal meningitis.

- Updated information and recommendations on the use of azole antifungals during pregnancy.

Cryptococcosis

- Updated alternative regimens for induction, consolidation, and maintenance therapy and recommendations on the timing and frequency of lumbar punctures for central nervous system and/or disseminated disease.

- Updated the recommended fluconazole dosing for the treatment of focal pulmonary infiltrates and isolated cryptococcal antigenemia.

- Provided more detailed recommendations for treatment during pregnancy.

Histoplasmosis

- Added alternative maintenance therapy regimens for treatment of severe disseminated disease.

- Updated information on the importance of monitoring serum concentration levels for itraconazole and voriconazole.

October 8, 2024

Bacterial Enteric Infections

- Updated information on antimicrobial resistance among bacterial enteric pathogens.

- Updated recommended regimens for empiric therapy pending susceptibility results, including a recommendation to consider empiric carbapenem therapy in people with advanced HIV and severe diarrhea where campylobacter bacteremia is suspected.

- Updated information on the use of antibiotics for bacterial enteric infections during pregnancy.

September 16, 2024

Candidiasis

- Added information on the role of ibrexafungerp in the treatment of vulvovaginal candidiasis and recurrent vulvovaginal candidiasis and the approval of ibrexafungerp by the U.S. Food and Drug Administration (FDA).

- Added information on the role of oteseconazole for the treatment of recurrent vulvovaginal candidiasis and the approval of oteseconazole by the FDA.

Pneumocystis Pneumonia

- Simplified indications for starting primary prophylaxis.

- Added intermittent intravenous pentamidine as an alternative regimen for primary or secondary prophylaxis.

- Provided more detailed recommendations for management during pregnancy.

Toxoplasmosis

- Recommended primarily limiting baseline serologic screening and measures to prevent exposure to individuals with CD4 T lymphocyte cell counts <200 cells/mm^3.

- Added trimethoprim-sulfamethoxazole as a preferred regimen for acute infection.

- Provided more detailed recommendations for management during pregnancy.

August 15, 2024

Disseminated Mycobacterium avium Complex Disease

- Updated information to prioritize the initiation of effective antiretroviral therapy (ART) and to refrain from primary prophylaxis for Mycobacterium avium Complex (MAC) except for people with HIV who are not receiving ART, remain viremic on ART, or have no options for a fully suppressive ART regimen.

- Added new information indicating that drugs demonstrating substantive in vitro activity against MAC might be considered for the treatment of refractory MAC disease (e.g., bedaquiline, tedizolid, linezolid, omadacycline), acknowledging that there is insufficient observational or clinical trial data to support formal recommendations in this setting.

- Updated information on drug–drug interactions between anti-MAC therapies, particularly rifabutin, and antiretroviral drugs and provided a link to the Adult and Adolescent Antiretroviral Guidelines on drug–drug interactions.

July 29, 2024

Leishmaniasis

- Updated information on prevalence, including transmission in the United States.

- Updated information on the use of polymerase chain reaction, or PCR, and serological tests for the diagnosis of leishmanial diseases.

- Updated treatment regimens for each of the leishmanial diseases, including regimens that reduce the likelihood of recurrence.

- Added new information about special considerations in pregnancy.

July 9, 2024

Human Papillomavirus Disease

- A brief summary of this update is available here from the NIH Office of AIDS Research.

- Based on the ANCHOR study results, provided new screening and treatment recommendations for anal cancer prevention.

- Provided new anal cancer screening algorithms.

Introduction

Opportunistic infections (OIs), which in the context of HIV have been defined as infections that are more frequent or more severe because of HIV-mediated immunosuppression,[1] were the first clinical manifestations that alerted clinicians to the occurrence of AIDS. *Pneumocystis* pneumonia (PCP), *Toxoplasma* encephalitis, cytomegalovirus retinitis, cryptococcal meningitis, tuberculosis, disseminated *Mycobacterium avium* complex (MAC) disease, and pneumococcal respiratory disease, as well as Kaposi sarcoma and central nervous system lymphoma cancers, have been hallmarks of AIDS. These OIs occurred, on average, 7 to 10 years after infection with HIV.[2,3] Until effective antiretroviral therapy (ART) was developed, patients generally survived only 1 to 2 years after the initial clinical manifestation of AIDS.[4]

Since the late 1980s, the use of chemoprophylaxis, immunization, and better strategies for managing OIs have improved the quality of life and lengthened the survival of people with HIV.[5] Profound reduction in OI-related morbidity and mortality in people with HIV resulted from the introduction of highly effective combination ART in the mid-1990s.[6-12]

Despite the availability and wide use of safe, effective, and simple ART regimens that have led to corresponding population-level declines in the incidence of OIs,[10,13,14] the Centers for Disease Control and Prevention (CDC) estimates that in 2022, 13% of people with HIV in the United States were unaware of their positive HIV status and 43% of Americans with HIV who were aware of their positive HIV status were not effectively virally suppressed (see Figure 14 and Table 5 in the CDC HIV Surveillance report).[15,16] As a result, OIs continue to cause preventable morbidity and mortality in the United States.

Achieving and maintaining durable viral suppression in all people with HIV and preventing or substantially reducing the incidence of HIV-related OIs remains challenging for three main reasons:

- *Not all HIV infections have been diagnosed, and once HIV is diagnosed, many people have already experienced substantial immunosuppression.* The CDC estimates that in 2022, among those with diagnosed HIV, approximately 21% had a CD4 T lymphocyte (CD4) cell count <200 cells/mm^3 (or <14%) at the time of diagnosis (see Figure 2 and Table 1a in the CDC HIV Surveillance report).[15]

- *Not all people with diagnosed HIV receive timely, continuous HIV care or are prescribed ART.* The CDC estimates that in 2022, 82% of people with newly diagnosed HIV had been linked to care within 1 month (see Figure 3 and Table 2a in the CDC HIV Surveillance report). However, only 47% of people with HIV were adequately engaged in continuous care (see Figure 14 in the CDC HIV Surveillance report).[15]

- *Not all people who are treated for HIV achieve durable viral suppression.* The CDC estimates that in 2022, only 65% of people were both engaged in care and had durable viral suppression within 6 months of HIV diagnosis (see Figure 11 in the CDC HIV Surveillance report).[15] Causes for the suboptimal response to treatment include challenges with adherence, unfavorable pharmacokinetics, or unexplained biologic factors.[17]

Thus, some people with HIV will continue to present with an OI as the sentinel event (leading to a diagnosis of HIV) or present with an OI as a complication of unsuccessful viral suppression.[15]

Durable viral suppression eliminates most but not all OIs. Tuberculosis, pneumococcal disease, and dermatomal zoster are examples of infectious diseases that occur at higher incidence in people with HIV regardless of CD4 count. The likelihood of each of these OIs occurring does vary inversely with the CD4 count, however.[18-24] Certain OIs—most notably tuberculosis and syphilis—can increase plasma viral load,[25-29] which both accelerates HIV progression and increases the risk of HIV transmission if patients are not virally suppressed by ART.

Therefore, clinicians continue to need to be knowledgeable about the prevention and management of HIV-related OIs.

History of These Guidelines

In 1989, the Guidelines for Prophylaxis Against *Pneumocystis carinii* Pneumonia for Persons Infected with the Human Immunodeficiency Virus became the first HIV-related treatment guideline published by the U.S. government.[30] This guideline was published in the *Morbidity and Mortality Weekly Report (MMWR)*, which was the most rapid mode of publication at the time. It was followed by a guideline on prevention of MAC disease in 1993.[31] In 1995, these guidelines were expanded to include the treatment of 18 HIV-related OIs. In 2004, information about the prevention of HIV-related OIs was incorporated into the guidelines. The National Institutes of Health (NIH), the HIV Medicine Association (HIVMA), and the Infectious Diseases Society of America (IDSA) jointly co-sponsor these guidelines,[1,32,33] which have been published in peer-reviewed journals and/or the *MMWR* in 1997, 1999, 2002, 2004, and 2009.[33-44] Since 2009, these OI guidelines have been managed as a living document on the web, with each chapter reviewed quarterly by the guidelines committee. Updates are published as often and as promptly as deemed appropriate by the guidelines committee.

In 2023, there were nearly 566,000 online page views and approximately 17,400 PDF downloads, which demonstrate that the Adult and Adolescent OI Guidelines continue to be a valuable resource to clinicians, other health care providers, people with HIV, and policymakers in the United States. Guidelines pertinent to other regions of the world, especially resource-limited countries, may differ with respect to the spectrum of relevant OIs and the diagnostic and therapeutic options that are available to clinicians.

All guideline recommendations related to prevention or treatment are rated based on rigorous criteria that include the quality of supporting evidence. These ratings allow readers to assess the relative importance of each recommendation.

These guidelines address the prevention and treatment of HIV-related OIs in adults and adolescents. Guidelines addressing the prevention and treatment of HIV-related OIs in pediatric populations can be found on the Clinicalinfo website.

Snapshot of Guidelines Development Process

These guidelines were prepared by the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) under the auspices of the Office of AIDS Research Advisory Council (OARAC), an authorized Federal Advisory Committee

to the U.S. Department of Health and Human Services established in 1994. Co-chairs who are selected and appointed by their respective agencies or organizations (i.e., NIH, IDSA, HIVMA) convene OI-specific working groups of clinicians and scientists with subject matter expertise in specific OIs.

The working groups review in real time the relevant literature published since the last review, with the help of quarterly literature searches for articles relevant to their section that are provided by guidelines support staff. The working groups propose revisions to their section as appropriate. The co-chairs, representatives from HIVMA and IDSA, and other Panel working groups with special expertise (e.g., pharmacology, pregnancy) review proposed revisions.

The co-chairs and working group leaders have quarterly teleconferences to discuss section updates. In addition, the co-chairs convene an annual meeting with members of the Panel to discuss guidelines content and strategic planning.

The names and affiliations of all contributors, as well as their financial disclosures, are provided in Appendix B: Panel Roster and Financial Disclosures.

Guidelines Development Process	
Topic	**Comment**
Goal of the guidelines	Provide guidance to HIV care practitioners and others on the optimal prevention and management of HIV-related opportunistic infections (OIs) for adults and adolescents in the United States.
Panel members	The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) is composed of co-chairs who represent the National Institutes of Health (NIH), the HIV Medicine Association (HIVMA), and the Infectious Diseases Society of America (IDSA), plus Panel members with expertise in HIV clinical care, infectious disease management, and research. Co-chairs are selected by their respective agencies or organizations. Each working group is led by a Panel member selected by the co-chairs. Panel members are selected from government, academia, and the health care community by the co-chairs and working group leaders based on the member's area of subject matter expertise. Members serve on the Panel for a 4-year term, with an option to be reappointed for additional terms. Prospective Panel members may self-nominate at any time. When specific or unique subject matter expertise is required, the co-chairs, together with working group leaders, may solicit advice from individuals with such specialized knowledge. The list of the current Panel members can be found in Appendix B: Panel Roster and Financial Disclosures.
Financial disclosure and management of conflicts of interest	All members of the Panel submit a written financial disclosure annually reporting any associations with manufacturers of drugs, vaccines, medical devices, or diagnostics used to manage HIV-related OIs. A list of these disclosures and their last update is available in Appendix B: Panel Roster and Financial Disclosures. The co-chairs review each reported association for potential conflicts of interest and determine the appropriate action: disqualification from the Panel, disqualification or recusal from topic review and discussion, or no disqualification needed. A conflict of interest is defined as any direct financial interest related to a product addressed in the section of the guideline to which a Panel member contributes content. Financial interests include direct receipt by the Panel member of payments, gratuities, consultancies, honoraria, employment, grants, support for travel or accommodation, or gifts from an entity having a commercial interest in that product. Financial interests also include direct compensation for membership on an advisory board, data safety monitoring board, or speakers' bureau. Compensation and support provided to a Panel member's university or institution (e.g., grants, research funding) is not considered a financial conflict of interest. The co-chairs strive to ensure that 50% or more of the members of each working group have no conflicts of interest.
Primary users of the guidelines	HIV treatment providers
Developer	Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV, a working group of the Office of AIDS Research Advisory Council (OARAC). See Appendix B: Panel Roster and Financial Disclosures.
Funding source	Office of AIDS Research (OAR), NIH
Evidence collection	The recommendations in the guidelines are based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or information prepared by the U.S. Food and Drug Administration or manufacturers (e.g., warnings to the public) may be used as evidence to revise the guidelines. Members of each working group are responsible for identifying relevant literature and conducting a systematic comprehensive review of literature that is provided to them on a quarterly basis.

Guidelines Development Process	
Topic	**Comment**
Method of synthesizing data and formulating recommendations	Each section of the guidelines is assigned to a working group of Panel members with expertise in the area of interest. The members of the working group synthesize the available data. Recommendations are reviewed and updated by each working group after an assessment of the quality and impact of the existing and any new data. Types of evidence that are considered include but are not necessarily limited to case series, prospective cohort trials, and randomized controlled trials, with consideration of the quality and appropriateness of the methods, and the number of participants and effect sizes observed. Finally, all proposed recommendations and supporting evidence are reviewed by the co-chairs before final approval and publication. OAR reviews all proposed recommendations and gives final approval.
Recommendation rating	Recommendations are rated according to the information in the table below, "Rating System for Prevention and Treatment Recommendations," and accompanied, as needed, by explanatory text that reviews the evidence and the working group's assessment. All proposed changes are discussed during teleconferences and by email and then assessed by the Panel's co-chairs and reviewed by OAR, HIVMA, and IDSA before being endorsed as official recommendations.
Other guidelines	These guidelines focus on prevention and treatment of HIV-related OIs for adults and adolescents. A separate guideline outlines similar recommendations for children who have HIV. These guidelines are also available on the Clinicalinfo website.
Update plan	Each working group leader and the co-chairs meet every 3 months by teleconference to review interim data that may warrant modification of the guidelines. Updates may be prompted by approvals of new drugs, vaccines, medical devices, or diagnostics; new information regarding indications or dosing; new safety or efficacy data; or other information that may affect prevention and treatment of HIV-related OIs.

How to Use the Information in These Guidelines

Recommendations in this report address—

- Preventing exposure to opportunistic pathogens;

- Preventing disease;

- Discontinuing primary prophylaxis after immune reconstitution;

- Treating disease;

- When to start ART in the setting of an acute OI;

- Monitoring for adverse effects (including immune reconstitution inflammatory syndrome);

- Managing treatment failure;

- Preventing disease recurrence (secondary prophylaxis or chronic maintenance therapy);

- Discontinuing secondary prophylaxis or chronic maintenance therapy after immune reconstitution; *and*

- Special considerations during pregnancy.

Recommendations are rated according to the criteria in the table below and accompanied, as needed, by explanatory text that reviews the evidence and the working group's assessment. In this system, the letters A, B, or C signify the strength of the recommendation for or against a preventive or therapeutic measure, and the Roman numerals I, II, or III indicate the quality of the evidence supporting the recommendation.

Rating System for Prevention and Treatment Recommendations	
Strength of Recommendation	Quality of Evidence for the Recommendation
A: Strong recommendation for the statement B: Moderate recommendation for the statement C: Weak recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes* III: Expert opinion*

* In cases where there are no data for the prevention or treatment of an opportunistic infection based on studies conducted in people with HIV but there are data derived from studies in people without HIV that could plausibly guide management of patients with HIV, the recommendation is rated II or III but is assigned A, B, or C depending on the strength of the recommendation.

This document also includes tables in each section pertinent to the prevention and treatment of the OI(s) in that section, as well as six summary tables at the end of the document (Tables 1–6).

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Bacterial Enteric Infections

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Epidemiology

HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase the risk of enteric bacterial infections. Rates of Gram-negative bacterial enteric infections are at least 10 times higher among adults with HIV than in the general population, but these rates are lower among people with HIV who are treated with antiretroviral therapy (ART).[1] The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) cell count and is greatest in individuals with clinical AIDS or CD4 counts <200 cells/mm^3.

The bacteria most frequently isolated by culture from adults with HIV in the United States are *Shigella*, *Campylobacter*, and nontyphoidal *Salmonella* spp. (particularly *Salmonella enterica* serotypes Typhimurium and Enteritidis).[1-6] Diarrheagenic *Escherichia coli*, particularly enteroaggregative *E. coli*, may contribute to the burden of diarrheal disease,[7] but their role is understood poorly because reporting to public health systems is not required. Data on *Helicobacter pylori* infection in HIV infection are limited and do not suggest excess risk in people with HIV.[8]

Clostridioides difficile–associated infection (CDI) is common in people with HIV[9]; in addition to traditional risk factors, such as exposure to a health care facility or to antibiotics, data[10] suggest that low CD4 count (<50 cells/mm^3) is an independent risk factor. Incidence of community-onset CDI is increasing, and clinicians also should consider CDI in the evaluation of outpatient diarrheal illnesses in people with HIV.

Other enteric infections that may cause diarrhea—such as *Mycobacterium avium* complex (MAC), cytomegalovirus, and various protozoa—are discussed elsewhere in these guidelines.

As with bacterial enteric infections in people without HIV, the probable source for most bacterial enteric infections in people with HIV is ingestion of contaminated food or water.[11] Sexual activity with the potential for direct or indirect fecal-oral exposure also increases risk of infections, especially with *Shigella*[12] and *Campylobacter*.[3,13-16]

Clinical Manifestations

Three major clinical syndromes of infection are associated with Gram-negative enteric bacteria among people with HIV:

- Self-limited gastroenteritis;

- Severe and prolonged diarrheal disease, potentially associated with fever, bloody diarrhea, and weight loss; *and*

- Bacteremia associated with extra-intestinal involvement, with or without concurrent or preceding gastrointestinal (GI) illness.[6,17,18]

Severe community-associated diarrhea often is defined as six or more loose stools (loose stool is defined as defecated material that takes the shape of a container) per day with or without other signs of systemic illness, such as fecal blood, orthostatic hypotension, or fever. In people with HIV, the risk of more profound illness increases with the degree of immunosuppression but risk diminishes

with ART therapy.[1,4,5,11,18,19] Relapses in infection with *Salmonella* and other Gram-negative bacterial enteric pathogens after appropriate treatment have been well documented in people with HIV.[11,20,21] As in other populations, CDI can cause a variety of syndromes, from watery diarrhea to toxic megacolon.[10]

Although enteric pathogens can be associated with clinical proctitis (e.g., pain with defecation, tenesmus, bloody discharge),[22] other infections that may be transmitted during intimate contact (e.g., *Chlamydia trachomatis* including lymphogranuloma venereum, *Neisseria gonorrhoeae,* herpes simplex virus, *Treponema pallidum,* and mpox) more commonly cause this syndrome, especially in those with relevant exposures (e.g., condomless receptive anal intercourse).[23] Proctocolitis with diarrhea caused by STIs is less common but may occur; relevant exposures should be queried.[24]

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history (i.e., ingestion of contaminated food or water, including through recreational exposure to water, sexual history or other fecal-oral exposures, animal/pet exposures, travel-related exposures, exposure to antibiotics or chemotherapies, use of acid-suppressing medications, recent hospitalization); a medication review, because diarrhea is a common side effect of some ART and antibiotics; quantification of the diarrheal illness by stool frequency, consistency, volume, duration, and presence of blood; and associated signs and symptoms, such as presence and duration of fever. Physical examination should include measurement of temperature and assessment of intravascular volume and nutritional status.

The diagnosis of Gram-negative bacterial enteric infection is established through cultures of stool and blood or stool molecular methods (i.e., culture-independent diagnostic tests [CIDTs]), ideally before antibiotics are given. Although stool molecular methods rapidly diagnose enteric infections, stool cultures are required to obtain phenotypic antibiotic sensitivity testing for isolated enteric pathogens and may also be helpful during outbreak investigations to identify the source. Thus, the Centers for Disease Control and Prevention (CDC) recommends reflex stool cultures and antibiotic sensitivity testing for specimens with positive CIDT reports given increasing resistance detected in enteric bacterial infections.[25] Because incidence of bacteremia associated with *Salmonella* gastroenteritis is high in people with HIV—particularly those with advanced disease—blood cultures should be obtained from any patient who has diarrhea and fever. For shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.[18]

Other infections for which people with HIV are at risk, albeit at a lower rate, are non-*jejuni,* non-*coli Campylobacter* spp.—such as *C. fetus, C. upsaliensis,* and *C. lari*—and the enterohepatic *Helicobacter* spp. (*H. cineadi* and *H. fennelliae)*, which were described originally as *Campylobacter* spp. Blood culture systems typically will grow these bacteria, but they are unlikely to be identified on routine stool cultures performed by most laboratories because growing these fastidious organisms requires special stool culture conditions.

The diagnosis of CDI can be made only through careful selection of the correct population for testing and a correlation of clinical and laboratory findings. Populations at risk for *C. difficile* diarrhea include individuals who recently received or currently are receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy; those who have been hospitalized in the past 4 to 6 weeks (or currently are hospitalized); those who reside in a long-term care facility; those with CD4 counts <200 cells/mm^3; those taking acid-suppressive medications; and those with moderate-to-severe community-acquired diarrhea.[26] Only people with diarrhea (defined as three or more loose stools in 24 hours) should be tested for CDI to limit detection of asymptomatic colonization, and only stool samples that take the shape of the container (i.e., diarrheal) should be tested.[27] Detection of

either the *C. difficile* toxin B gene (using nucleic acid amplification testing [NAAT]) or the *C. difficile* toxin B protein (using an enzyme immunoassay [EIA]) is required for diagnosis. Current EIAs suffer from low sensitivity, whereas polymerase chain reaction (or PCR) assays have high sensitivity and can detect asymptomatic carriers. Glutamate dehydrogenase (GDH) antigen enzyme immunoassays, which detect an antigen common to *C. difficile* strains, whether or not toxigenic, must be combined with a second confirmatory test for stool *C. difficile* toxin B.[28,29] Based on the criteria above (i.e., person meets the definition of diarrhea and the stool sample is diarrhea, taking the shape of the container), Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (or SHEA) guidelines for CDI support using an NAAT alone or a multiple-step algorithm (e.g., GDH plus toxin B assay) versus an EIA alone for *C. difficile* testing.[29]

Endoscopy generally should be reserved for patients in whom stool culture, microscopy, *C. difficile* toxin B assay, and blood culture fail to reveal an etiology or in whom treatment for an established diagnosis fails. Endoscopy with biopsy may be required for diagnosing etiologies other than bacterial enteric infections—including cryptosporidiosis, microsporidiosis, cytomegalovirus, or MAC gastroenteritis—and noninfectious causes of GI symptoms.

Clinicians should remain alert to the possibility of sexually transmitted infections (STIs). In patients with relevant exposures and symptoms of proctitis or proctocolitis, diagnostic evaluation and treatment for STIs should are recommended.[30]

Preventing Exposure

Multiple epidemiologic exposures can place people at risk for enteric illnesses. The most common are ingestion of contaminated food or water and fecal-oral exposures. Providing advice and education about such exposures is the responsibility of the health care provider. The clinical condition and CD4 count of a person with HIV can help the provider determine what prevention recommendations are most appropriate. People with HIV with CD4 counts <200 cells/mm^3 or a history of AIDS-defining illness[31] are at the greatest risk of enteric illnesses; however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Individuals in the community should be advised to wash their hands regularly with soap and water or alcohol-based cleansers to reduce the risk of enteric infection **(AIII).** To prevent enteric infections, soap and water are preferred over alcohol-based cleansers, which do not kill *C. difficile* spores and are active only partially against norovirus and *Cryptosporidium* **(AIII).** People with HIV should be advised to wash their hands with soap and water after potential contact with human feces (e.g., through defecation, sexual exposures, cleaning feces from infants, contact with a person who has diarrhea), after handling pets or other animals, after gardening or other contact with soil, and before preparing food and eating **(AIII).** In addition to handwashing, use of barriers (e.g., condoms, dental dams, and gloves) can reduce exposure to feces when engaging in sex practices such as anal sex and oral-anal contact **(AIII).**[22,30,32] Avoiding sex while any partner has diarrhea may further reduce risk of transmission. Travelers to relevant locations may be counseled on food and water hygiene (see the CDC Travelers' Health webpage).[33]

Preventing Disease

Recommendations for Preventing Bacterial Enteric Infections
Preventing Bacterial Enteric Illness
• Immunizations (e.g., against *Salmonella serotype* Typhi) should be recommended in advance of travel to relevant locations (see Immunizations for Preventable Diseases in Adults and Adolescents With HIV in the Adult and Adolescent Opportunistic Infection Guidelines) **(AIII)**.
• Antimicrobial prophylaxis to prevent bacterial enteric illness **is not routinely recommended,** including for travelers **(AIII)**.
• In rare cases—such as for immunosuppressed travelers (depending on their level of immunosuppression, the region of travel, and the trip's duration)—antimicrobial prophylaxis with rifaximin or azithromycin should be offered **(CIII)**.
• Because of toxicity associated with fluoroquinolone use (e.g., CDI, tendinitis) and increasing rates of antimicrobial resistance among enteric bacterial pathogens outside of the United States, routine use of fluoroquinolones for prophylaxis is discouraged **(AIII)**.
• For pregnant people, azithromycin is the preferred agent for prophylaxis **(BIII)**.

Key: CDI = *Clostridioides difficile*–associated infection

Antimicrobial prophylaxis to prevent bacterial enteric illness **is not routinely recommended,** including for travelers **(AIII).** Prophylactic antimicrobial treatment can elicit adverse reactions, promote the emergence of resistant organisms, and increase the risk of CDI. In rare cases, however, antimicrobial prophylaxis (e.g., with rifaximin or azithromycin) should be considered—such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration **(CIII).**[34,35] In addition, immunizations, (e.g., against *Salmonella* serotype Typhi), should be recommended in advance of travel to relevant locations (see Immunizations for Travel in the Immunizations section of the Adult and Adolescent Opportunistic Infection Guidelines) **(AIII).**

For people with HIV already taking trimethoprim-sulfamethoxazole (TMP-SMX) (e.g., for *Pneumocystis jirovecii* pneumonia prophylaxis), TMP-SMX may offer limited protection against traveler's diarrhea.[36] For pregnant people, azithromycin would be the preferred agent for prophylaxis **(BIII).** Clinicians should be aware of concerns about fluoroquinolone safety. Given increased recognition of fluoroquinolone toxicities, as well as increasing rates of antimicrobial resistance among enteric bacterial pathogens outside the United States, routine use of fluoroquinolones for prophylaxis is discouraged **(AIII).**[37]

Treating Disease

Recommendations for Treating Bacterial Enteric Infections
General Considerations When Managing Patients With Bacterial Enteric Infections
• Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhea **(AIII)**.
• Antimotility agents should be avoided if concern about inflammatory diarrhea, including CDI, exists **(BIII)**.
• Diagnostic fecal specimens should be obtained before initiation of empiric antimicrobial therapy.
• If a pathogen is identified in stool, antibiotic susceptibilities should be performed to confirm and inform antibiotic choice given increased reports of antibiotic resistance. Reflexively culturing the stool of patients diagnosed using PCR-based methods can facilitate antibiotic susceptibility testing among these patients.

- Risk of a bacterial enteric infection increases as CD4 count declines, with the greatest risk in people with CD4 counts <200 cells/mm³. Risk of bacteremia also increases with decreasing CD4 count. If no clinical response occurs after 3 to 4 days of therapy, consider follow-up stool culture with antibiotic susceptibility testing and other methods to detect enteric pathogens (e.g., toxin assays, molecular methods), alternative diagnosis, antibiotic resistance, or drug–drug interactions (BIII).

- Effective ART may reduce the frequency, severity, and recurrence of bacterial enteric infections.

Empiric Treatment of Bacterial Enteric Infections
(Pending Diagnostic Studies and Antimicrobial Resistance Testing)

For People With HIV and CD4 >500 cells/mm³, With 1–2 Days of Loose Stools Without Fever or Blood

- Oral hydration; no further work-up and no treatment is needed.

For People With HIV and CD4 Count 200–500 cells/mm³, With Diarrhea Severe Enough to Compromise Quality of Life or Ability to Work

- Azithromycin 500 mg PO daily for 5 days (BIII), *or*

- Ciprofloxacin 500–750 mg PO every 12 hours for 5 days (BIII)

For People With HIV and Severe Disease (e.g., people with CD4 count <200 cells/mm³ or concomitant AIDS-defining illnesses), With Clinically Severe Diarrhea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills)

- Hospitalization for inpatient diagnostic evaluation and IV antibiotics

- Ceftriaxone 1–2 g IV every 24 hours (BIII)[a] until antimicrobial susceptibility is available, then treatment can be changed based on sensitivity results.

  o If *Campylobacter* or *Shigella* bacteremia is suspected, a carbapenem is preferred for empiric therapy (BIII).

Duration of Therapy

- Therapy and its duration should be adjusted depending on stool microbiology results and antibiotic sensitivity testing. See recommendations for specific bacteria below. If no pathogen is identified and the patient recovers quickly, 5 days of therapy is recommended.

Other Considerations

- MSM may be at increased risk for antibiotic-resistant enteric infections.

- Diarrhea is a common illness of international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is common. Clinicians should consider the possibility of resistant infections when prescribing empiric antibiotic therapy for travelers with HIV while traveling or upon return to the United States, particularly among travelers to South and Southeast Asia or Africa.

- For patients with persistent diarrhea (>14 days) but no other severe clinical signs (e.g., dehydration, blood in stool), antibiotic therapy can be withheld until a diagnosis is confirmed. Noninfectious etiologies of persistent diarrhea (e.g., inflammatory bowel disease) also can be considered in the differential diagnosis (BIII).

- Azithromycin should not be used to treat bacteremia.

- Before susceptibilities are known, empiric IV ceftriaxone is recommended, although given the rise of antimicrobial resistance in enteric pathogens, updated outbreak information, local susceptibility patterns, and travel history should always be considered.

Treating Nontyphoidal Salmonellosis

All people with HIV and salmonellosis should receive antibiotic treatment due to the increased risk of bacteremia (by 20- to 100-fold) and mortality (by as much as sevenfold) compared with people without HIV (AIII).

For Invasive Disease (Suspected or Confirmed) Pending Susceptibilities

- Ceftriaxone 1–2 g IV every 24 hours pending susceptibilities (BIII)

Preferred Therapy for Nontyphoidal Salmonella Gastroenteritis With or Without Bacteremia (If Susceptible)

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours **(AIII)**

Alternative Therapy (If Susceptible)

- Levofloxacin 750 mg (PO or IV) every 24 hours **(BIII)**, *or*

- Moxifloxacin 400mg (PO or IV) every 24 hours **(BIII)**, *or*

- Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) every 12 hours **(BIII)**, *or*

- Ceftriaxone 1–2 g IV every 24 hours **(BIII)**

Duration of Therapy for Gastroenteritis Without Bacteremia

- If CD4 count ≥200 cells/mm^3: 7–14 days **(BIII)**

- If CD4 count <200 cells/mm^3, minimum of 2 weeks (may extend to up to 6 weeks if with severe disease or bacteremia) **(BIII)**

Duration of Therapy for Gastroenteritis With Bacteremia

- If CD4 count ≥200 cells/mm^3: 14 days; longer duration if bacteremia persists or if the infection is complicated (e.g., metastatic foci of infection are present) **(BIII)**

- If CD4 count <200 cells/mm^3: 2–6 weeks **(BIII)**

Secondary Prophylaxis

- The role of long-term, secondary prophylaxis for patients with recurrent bacteremia or gastroenteritis is not well established. Clinicians must weigh the benefit against the risks of long-term antibiotic exposure **(BIII)**. Antibiotic choices for secondary prophylaxis are the same as for primary treatment and are dependent on the sensitivity of the *Salmonella* isolate.

- HIV suppression with ART is expected to decrease the risk of recurrent illnesses.

- Clinicians should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Indication

- Patients with recurrent bacteremia **(BIII)**, *or*

- Patients with recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 and severe diarrhea **(BIII)**

Discontinuing Secondary Prophylaxis

- After resolution of *Salmonella* infection and response to ART with sustained viral suppression and CD4 count >200 cells/mm^3, secondary prophylaxis likely can be discontinued **(CII)**.

Treating Shigellosis

Therapy should be considered because it may slightly shorten the duration of illness and help prevent spread of the infection to others **(AIII)**; however, antibiotic selection should be guided by the results of antibiotic susceptibility testing. Because antimicrobial resistance of *Shigella* spp. is increasing and limited data demonstrate that antibiotic therapy limits transmission, antibiotic treatment may be withheld in people with HIV and CD4 >500 cells/mm^3 whose diarrhea resolves before culture confirmation of *Shigella* infection **(CIII)**.

In Severely Ill Patients Requiring Empiric Parenteral Therapy While Awaiting Susceptibility

- Initiate a carbapenem until antimicrobial susceptibilities are available **(BIII)**.

Preferred Therapy (If Susceptible)

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours if MIC <0.12 µg/mL for 5 to 10 days **(AIII)**

Alternative Therapy (If Susceptible)

- Levofloxacin 750 mg (PO or IV) every 24 hours if MIC <0.12 ug/mL for 5 to 10 days **(BIII)**, *or*

- Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV every 12 hours for 5 to 7 days **(BIII)**, *or*

  - Note: TMP-SMX **is not recommended** for bacteremia.

- Azithromycin 500 mg PO daily for 5 days **(BIII)**

  - Note: Azithromycin **is not recommended** for bacteremia **(AIII)**

- Ceftriaxone 1–2 g IV every 24 hours **(BIII)**

Duration of Therapy

- Gastroenteritis: 5–7 days **(AIII)** (except ciprofloxacin [5 to 10 days] and azithromycin [5 days])

  - 7–10 days of therapy may be reasonable in patients who are severely immunosuppressed with poor clinical response to antibiotics.

- Bacteremia: ≥14 days **(BIII)**

- Recurrent infections: up to 6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy

- **Not recommended** for first-time *Shigella* infections **(BIII)**

Treating Campylobacteriosis

- Optimal treatment is poorly defined and multidrug resistance may occur.

- Antimicrobial therapy should be modified based on susceptibility reports.

Mild Disease If CD4 Count >200 cells/mm^3

- If diarrhea resolves before culture confirmation of *Campylobacter* infection, antibiotic treatment can be withheld **(CIII)**. If symptoms persist for more than several days, consider antibiotic therapy **(CIII)**.

Mild-to-Moderate Disease

- *Preferred Therapy (If Susceptible)*

  - Azithromycin 500 mg PO daily for 5 days **(BIII)** (**not recommended** for bacteremia **[AIII]**), *or*

  - Ciprofloxacin[b] 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days **(BIII)** (if susceptible)

- *Alternative Therapy (If Susceptible)*

  - Levofloxacin[c] 750 mg PO or IV every 24 hours **(BIII)**, *or*

Bacteremia

- Ciprofloxacin[b] 500–750 mg PO (or 400 mg IV) every 12 hours for ≥14 days **(BIII)** (if susceptible) plus an aminoglycoside **(BIII)** to limit the emergence of antibiotic resistance

Duration of Therapy

- Gastroenteritis: 7–10 days (except azithromycin, which is 5 days) **(BIII)**

- Bacteremia: ≥14 days **(BIII)**

- Recurrent disease: 2–6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy

- Not recommended for first-time *Campylobacter* infections **(BIII)**

[b] The rate of fluoroquinolone resistance in the United States is increasing (29% resistance in 2018 among *C. jejuni* isolates). Third generation cephalosporins are not reliably active and use of alternative cell-wall active agents such as carbapenems may be necessary in severely ill people requiring empiric parenteral therapy until antimicrobial susceptibilities return.

Treating *Clostridioides difficile*–Associated Infection

Preferred Therapy (Severe or Nonsevere CDI[c])

- Fidaxomicin 200 mg PO two times per day for 10 days **(AI)**

Alternative Therapy

- Vancomycin 125 mg PO four times per day for 10 days **(AI)**

- For severe, life-threatening CDI, see *C. difficile* and references for additional information.

Alternative Therapy for Nonsevere CDI[c]

- If neither fidaxomicin nor vancomycin is available: metronidazole 500 mg PO three times per day for 10 days **(CI)**.

Note: Based on clinical trials, vancomycin is superior to metronidazole for therapy of CDI (discussed in text).

Recurrent CDI

- Use of fidaxomicin over oral vancomycin is recommended, in agreement with the 2021 IDSA CDI Guidelines, as it has a greater likelihood for a sustained clinical response at 30 days **(AI)**.

- Vancomycin is an acceptable option (see IDSA Guideline for tapered and pulsed regimens) **(AI)**.

- FMT may be considered after three CDI episodes (i.e., an initial and two recurrent episodes) **(CIII)**.

[c] Severe CDI: white blood cell count ≥15,000 cells/mL or serum creatinine concentrations >1.5 mg/dL; nonsevere CDI: white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL

Treating Bacterial Enteric Infections During Pregnancy

- Based on their safety profile, expanded-spectrum cephalosporins (such as ceftriaxone and cefotaxime) or azithromycin should be the first-line therapy for bacterial enteric infections during pregnancy if antimicrobials are required, depending on the organism and the results of susceptibility testing **(BIII)**.

- Other commonly prescribed antimicrobials during pregnancy include vancomycin and metronidazole. Fidaxomicin, quinolones, and TMP-SMX should be prescribed using shared decision-making.

- Quinolones can be used for bacterial enteric infections in pregnant people with HIV if indicated by susceptibility testing or failure of first-line therapy **(BIII)**.

- TMP-SMX use in the first trimester should be avoided, if possible, because of an association with an increased risk of birth defects, specifically neural tube, cardiovascular, and urinary tract defects **(BIII)**. Clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX if they are capable of becoming pregnant prior to pregnancy or as soon as possible in their first trimester **(BIII)**.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDI = *Clostridioides difficile*–associated infection; FMT = fecal microbiota therapy; IDSA = Infectious Diseases Society of America; IV = intravenously; MIC = minimum inhibitory concentration; MSM = men who have sex with men; PCR = polymerase chain reaction; PO = orally; TMP-SMX = trimethoprim-sulfamethoxazole

Empiric Therapy

In most situations, treatment of diarrheal disease in people with HIV does not differ significantly from that in immunocompetent individuals. Decisions on therapy are based on an assessment of diarrhea severity and hydration status. Patients should be informed of the importance of maintaining

hydration and be given oral or intravenous (IV) rehydration, if indicated **(AIII).** Because diarrheal disease can produce temporary malabsorption or lactose intolerance, consuming a bland diet and avoiding fat, dairy, and complex carbohydrates are likely to be useful and are therefore recommended **(BIII).** The effectiveness and safety of probiotics or antimotility agents have not been studied adequately in people with HIV who have diarrheal illnesses.[38] Antimotility agents should be avoided if concern about inflammatory diarrhea, including CDI, exists **(BIII).**

After obtaining stool samples for diagnostic evaluation, the initiation and duration of empiric antimicrobial therapy depend on the patient's CD4 count and clinical appearance. If stool samples are obtained, antibiotic susceptibility testing should be performed to confirm and inform antibiotic choice. For example, in patients with CD4 counts >500 cells/mm^3 who have had 1 to 2 days of loose stools without fever or blood, no further work-up and no treatment other than oral rehydration may be required. However, a short course of antibiotics (e.g., ciprofloxacin for 5 days **[BIII]**) may be indicated in people with HIV and CD4 counts of 200 to 500 cells/mm^3 who have diarrhea severe enough to compromise quality of life or ability to work. Patients with severe disease (advanced HIV disease [i.e., CD4 counts <200 cells/mm^3 or concomitant AIDS-defining illness] and clinically severe diarrhea [i.e., ≥6 liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease]) should undergo inpatient diagnostic evaluation to determine the etiology of the diarrheal illness and receive parenteral antimicrobial treatment **(AIII).** In stable patients, empiric therapy with oral ciprofloxacin **(BIII)** or azithromycin **(BIII)** is recommended, particularly if the infection is not associated with international travel. However, even in the United States, all patients should have careful follow-up since rates of resistance to ciprofloxacin and (to a lesser extent) azithromycin in common enteric pathogens are substantial, and therefore treatment failure may occur. In patients with severe disease, treatment with empiric IV ceftriaxone is recommended until antimicrobial susceptibility results are available **(BIII).** Given the rise of antimicrobial resistance in enteric pathogens, however, updated outbreak information, local susceptibility patterns and travel history always should be considered. For example, if *Campylobacter* or *Shigella* bacteremia is suspected, a carbapenem is preferred for empiric therapy **(BIII).**

Therapy should be adjusted based on the results of the diagnostic work-up. For diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity—such as bloody stool or dehydration—antibiotic therapy can be withheld and directed therapy initiated once a diagnosis is confirmed. Noninfectious etiologies of persistent diarrhea (e.g., inflammatory bowel disease) also should be considered in the differential diagnosis **(BIII).**

International travel: Diarrhea is one of the most common illnesses affecting international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is an important public health problem. For example, traveler's diarrhea caused by fluoroquinolone-resistant *C. jejuni* in South and Southeast Asia or Africa is common.[39,40] Clinicians should consider the possibility of a resistant infection when prescribing empiric therapy for travelers with HIV who experience diarrhea or a syndrome consistent with a systemic infection while traveling or upon returning to the United States, given reports of multidrug-resistant *Enterobacteriaceae* acquisition during travel.[41-45]

Pathogen-Specific Therapy

Nontyphoidal *Salmonella* Species

Immunocompetent hosts who do not have HIV often do not require antibiotic treatment for *Salmonella* gastroenteritis (typically caused by nontyphoidal *Salmonella* spp.) because the condition is usually self-limited, and treatment may prolong the carrier state. In contrast, all people with HIV

and salmonellosis should be treated **(AIII),** even though no clinical trials have compared antimicrobial therapy with placebo. Notably, HIV infection increases the risk of *Salmonella* bacteremia 20 to 100 times and mortality as much as seven times compared to people who do not have HIV.[19,46]

The treatment of choice for susceptible nontyphoidal *Salmonella* spp. infection is a fluoroquinolone **(AIII).** Ciprofloxacin is the preferred agent **(AIII).**[47] Other fluoroquinolones—such as levofloxacin and moxifloxacin are recommended as alternatives to ciprofloxacin **(BIII).** Although they have not been well evaluated in clinical trials, they likely would be effective in treating salmonellosis in people with HIV**.** Depending on antibiotic susceptibility, alternatives to the fluoroquinolones include TMP-SMX or expanded-spectrum cephalosporins, such as ceftriaxone **(BIII).** Fluoroquinolone resistance in nontyphoidal *Salmonella* spp. appears to be increasing, with preliminary CDC data showing genetic markers of fluoroquinolone resistance among 19% of 20,831 nontyphoidal *Salmonella* spp. isolates tested in the United States in 2023.[48] In agreement with IDSA guidelines, the Panel recommends ceftriaxone over ciprofloxacin if invasive disease is suspected or confirmed, at least until susceptibilities return **(BIII).**[47,48]

The optimal duration of therapy for HIV-related nontyphoidal *Salmonella* infection has not been defined. For patients with CD4 counts ≥200 cells/mm^3 who have mild gastroenteritis without bacteremia, 7 to 14 days of treatment is recommended **(BIII).** For the same patients with bacteremia, 14 days is appropriate provided clearance of bacteremia is documented. Longer treatment is recommended if bacteremia persists or if the infection is complicated (i.e., if metastatic foci are present) **(BIII).**

For any patients with advanced HIV disease (CD4 count <200 cells/mm^3) and *Salmonella* infection, a minimum of 2 weeks with extension up to 6 weeks of antibiotics in severe disease or bacteremia is often recommended **(BIII).**[49]

People with HIV and *Salmonella* bacteremia, which typically occurs in those with advanced HIV disease, should be monitored clinically for recurrence after treatment **(BIII).** As people with HIV age, it is also important to remember that rates of invasive *Salmonella* infections increase with age in each age group beyond infancy.[50,51] Recurrence may present as bacteremia or as an anatomically localized infection, including intraabdominal, endothelial, urinary tract, soft tissue, bone and joint, lung, or meningeal foci. Secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII),** and it also might be considered for patients with recurrent gastroenteritis (with or without bacteremia), and in those with CD4 counts <200 cells/mm^3 with severe diarrhea **(BIII).** The value of this secondary prophylaxis has not been established and must be weighed against the risks of long-term antibiotic exposure. Recurrent *Salmonella* bacteremia constitutes an AIDS-defining illness,[31] and HIV suppression with ART appears to decrease the risk of recurrent illnesses.

In patients whose *Salmonella* infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts >200 cells/mm^3, secondary prophylaxis for salmonellosis likely can be discontinued **(CII).** Clinicians also should be aware that recurrence may indicate development of antimicrobial resistance during therapy.

Shigella Species

Therapy for *Shigella* infections should be considered because it may slightly shorten the duration of illness and help prevent transmission to others **(AIII);** however, because antimicrobial resistance of *Shigella* spp. is increasing and limited data demonstrate that antibiotic therapy limits transmission,

antibiotic treatment may be withheld in people with HIV and CD4 >500 cells/mm^3 with mild symptoms or whose diarrhea is resolving before culture confirmation of *Shigella* infection **(CIII).** When treatment is offered, antibiotic selection should be guided by the results of antibiotic susceptibility testing.[43,52-55]

Preferred treatment for susceptible shigellosis is a fluoroquinolone, preferably ciprofloxacin, for 5 to 10 days **(AIII)** with levofloxacin serving as an alternative **(BIII).** Importantly, preliminary CDC data estimate 60% of *Shigella* spp. isolated among the general U.S. population in 2023 harbored genetic markers of resistance to ciprofloxacin, and 55% of such isolates tested in 2022 had a ciprofloxacin minimum inhibitory concentration (MIC) of ≥0.12 µg/mL.[48] Although current Clinical and Laboratory Standards Institute criteria categorize *Shigella* isolates with a ciprofloxacin MIC of 0.12 and 0.25 µg/mL as susceptible and a MIC of 0.5 µg/mL as intermediate, these isolates typically harbor a fluoroquinolone resistance gene or mutation. Until the clinical significance of these findings can be determined, alternative antibiotics should be considered to treat patients whose isolates have ciprofloxacin MICs ≥0.12 µg/mL **(BIII).**[56] In general, automated antimicrobial susceptibility test panels do not have doubling dilutions that span the MIC range to determine susceptibility to ciprofloxacin based on the CDC recommendation of ≤0.06. As such, a clinically validated manual antimicrobial susceptibility testing method such as reference broth microdilution or a gradient diffusion method would be required to confirm susceptibility at the lower MIC range. Ciprofloxacin-resistant *S. sonnei* and *S. flexneri* infections in the United States are associated with international travel, homelessness, and men who have sex with men (MSM); ciprofloxacin-resistant shigellosis among MSM appears to be acquired predominantly within the United States, rather than during travel.[43]

Depending on antibiotic susceptibilities, in stable patients without concern for bacteremia, azithromycin (5 days) or TMP-SMX (5–7 days) may be alternatives **(BIII).** Azithromycin has not been evaluated in people with HIV and shigellosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[56] Azithromycin susceptibility testing is not widely available in clinical laboratories but can be performed by many state public health laboratories. Preliminary CDC data estimate 34% of *Shigella* spp. isolated among the general U.S. population in 2023 harbored genetic markers of resistance to azithromycin.[48] Azithromycin-resistant *Shigella* spp. infections in MSM with HIV have been reported.[57-59]

Multidrug resistance is common among shigellae, and clinicians should be aware that rates of infections caused by extensively drug resistant *Shigella* strains (strains resistant to azithromycin, ciprofloxacin, ceftriaxone, trimethoprim-sulfamethoxazole, and ampicillin) are increasing in the United States.[60] Therefore, while IV ceftriaxone is recommended therapy for susceptible *Shigella*, in severely ill people requiring empiric parenteral therapy, carbapenems can be initiated before antimicrobial susceptibilities are available **(BIII).**

Treatment for people with *Shigella* bacteremia is less well defined but extending treatment to at least 14 days is recommended **(BIII).** Azithromycin **is not recommended** for treatment of *Shigella* spp. bacteremia **(AIII).** Chronic suppressive or maintenance therapy **is not recommended** for first-time *Shigella* infections **(BIII).** Recurrent infections can occur, particularly in individuals with CD4 counts <200 cells/mm^3, in which case, extending antimicrobial therapy for up to 6 weeks is recommended **(BIII).** Because of *Shigella's* extremely low infectious dose, patients with shigellosis should be counseled about transmission prevention. As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent shigellosis.

Campylobacter Species

The optimal treatment of campylobacteriosis in people with HIV is poorly defined and multidrug resistance might occur.[61,62] Culture and testing for the antibiotic susceptibility of *Campylobacter* isolates is recommended **(BIII).** In the United States in 2018, 29% of *C. jejuni* isolates were resistant to ciprofloxacin, and 2% were resistant to azithromycin; among *C. coli* isolates, 41% of isolates were resistant to fluoroquinolones, and 13% were resistant to azithromycin.[48]

For people with mild disease and CD4 counts >200 cells/mm^3, therapy should be withheld unless symptoms persist for more than several days **(CIII).** For mild-to-moderate campylobacteriosis, initiating therapy with azithromycin for 5 days or a fluoroquinolone—such as ciprofloxacin—for 7 to 10 days (if the organism is sensitive) is recommended **(BIII).** Azithromycin has not been evaluated in people with HIV and campylobacteriosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[39] Azithromycin susceptibility testing, however, is not widely available in clinical laboratories but can be performed by many state public health laboratories. *Campylobacter* bacteremia should be treated for at least 14 days using a fluoroquinolone if the isolate is sensitive **(BIII).**[63] Adding a second active agent—such as an aminoglycoside—may be prudent in patients with bacteremia to limit the emergence of antibiotic resistance **(BIII).** Third generation cephalosporins are not reliably active and use of alternative cell-wall active agents such as carbapenems may be necessary in severely ill people requiring empiric parenteral therapy until antimicrobial susceptibilities return. Antibiotic choice should be guided by antibiotic susceptibility tests. Azithromycin **is not recommended** for treatment of *Campylobacter* bacteremia **(AIII).** Chronic suppressive or maintenance therapy **is not recommended** for first-time *Campylobacter* infections in people with HIV **(BIII).** However, recurrent infections can occur, particularly in people with CD4 counts <200 cells/mm^3. In recurrent disease, extending the length of antimicrobial therapy for 2 to 6 weeks is reasonable **(BIII).** As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent *Campylobacter* spp. infections.[64]

Clostridioides difficile

No randomized controlled trials have been conducted for CDI therapy in people with HIV. Available data suggest that people with HIV respond to treatment of CDI similarly to people without HIV.[9] Thus, treatment of CDI in people with HIV is the same as in people without HIV. Guidelines and subsequent updates for treatment of CDI have been published[29,65] and should be consulted for further information.

Treatment of an Initial Episode of Clostridioides difficile–Associated Infection

Four randomized clinical trials all conducted in the general population (two identical studies with ~60% hospitalized patients; two studies restricted to hospitalized patients)[66-69] have revealed that, when compared to oral vancomycin, fidaxomicin increased the likelihood of a sustained clinical response of CDI (at 28 days) in the initial therapy of CDI (relative risk [RR] 1.16; 95% confidence interval [CI], 1.09–1.24).[65] Fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events and all-cause mortality. Given these data, the 2021 IDSA CDI Clinical Practice Guideline update[65] for adults suggests treatment with fidaxomicin rather than oral vancomycin, for initial CDI whether CDI is severe or nonsevere. Fidaxomicin remains very expensive but should be considered in people with HIV and CDI, if available **(AI).** Oral vancomycin is also an acceptable option for initial CDI **(AI).** Earlier multicenter, randomized, double-blind studies identified that oral vancomycin is superior to metronidazole for treatment of CDI.[70,71] Thus, metronidazole is to be considered as an alternative drug for CDI therapy only if fidaxomicin or

vancomycin are unavailable and CDI is nonsevere (white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL) **(CI).**[29]

Treatment of Recurrent Clostridioides difficile–Associated Infection

Treatment of recurrent CDI is complex and, in part, defined by the specific circumstances of the patient with recurrent CDI and the number of prior CDI episodes. Brief guidance is provided here; the 2017 and 2021 IDSA CDI guidelines should be consulted for a full discussion of this topic.[29,65] Risk factors for CDI recurrence are age ≥65 years, history of CDI, compromised immunity, severe CDI, and certain virulent strains (ribotypes 027/078/244). Similar to an initial episode of CDI and also based on the randomized clinical trials cited above,[66-69] the Panel recommends administering fidaxomicin, instead of oral vancomycin, to adults with recurrent CDI **(AI),** consistent with the 2021 IDSA CDI Clinical Practice Guideline update.[65] Fidaxomicin therapy increased the likelihood of a sustained clinical response for recurrent CDI at 30 days (RR 1.27; 95% CI, 1.05–1.54). For treatment of an initial CDI recurrence, fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events, and all-cause mortality. Vancomycin is also an acceptable option for recurrent CDI (see the IDSA Guideline for tapered and pulsed regimens) **(AI).**

Bezlotoxumab is a humanized monoclonal antibody against *C. difficile* toxin B approved for prevention of recurrent CDI in high-risk adults when used in conjunction with standard-of-care (SOC) antibiotic therapy. The 2021 IDSA CDI Clinical Practice Guideline update suggests use of bezlotoxumab as a cointervention along with vancomycin as the SOC antibiotic in patients with a history of CDI in the last 6 months or other risk factors for recurrence (i.e., age ≥65 years, compromised immunity, severe CDI, or certain virulent strains (ribotypes 027/078/244).[65] However, data on the benefit of bezlotoxumab therapy when fidaxomicin is used as the SOC antibiotic are limited. Limited case reports suggest that fecal microbiota therapy (FMT) (i.e., fecal transplant) may be successful and safe to treat recurrent CDI in people with HIV.[72-74] However, it is important to note that complications of FMT, including transmission of enteric pathogens and antibiotic-resistant bacteria with deaths, have been reported.[75,76] FMT for treatment of recurrent CDI may be considered after three total CDI episodes (initial and two recurrent CDI episodes) **(CIII).**[29,65] The effect of ART on recurrence of CDI is unknown, but ART initiation should follow standard guidelines, similar to other enteric infections (see the Special Considerations Regarding ART Initiation section below).

Special Considerations Regarding ART Initiation

ART initiation should follow standard guidelines. The presence of an enteric infection should not delay ART initiation **(AIII).** The presence of a diarrheal illness is relevant only in terms of a patient's ability to ingest and absorb ART. If recurrent enteric infections are documented or *Salmonella* bacteremia occurs, prompt initiation of ART should be considered regardless of CD4 count.

Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome)

Patients should be monitored closely for response to treatment, defined clinically by improvement in systemic signs and symptoms, resolution of diarrhea, and sterilization of infected tissues or body fluids, such as blood. Follow-up stool testing may be required when public health considerations and state policies dictate the need to ensure microbiologic cure, such as in health care or food service workers. Follow-up stool culture and antibiotic susceptibility testing should be considered for patients with incomplete clinical response to appropriate antimicrobial therapy. In patients with persistent or recurrent diarrhea despite therapy, clinicians should consider other enteric infections (including STIs; see the Diagnosis section above) in the context of the patient's immune status and

exposures, as well as the possibility of *C. difficile* or the development of antimicrobial resistance **(BIII).**

Observational studies suggest that plasma drug concentrations in people with HIV may be decreased as a result of severe diarrhea or malabsorption.[77,78] Coadministration of fluoroquinolones with magnesium- or aluminum-containing antacids or with calcium, zinc, or iron should be avoided because these agents interfere with fluoroquinolone absorption **(AII).**[79] Although larger prospective studies are needed to determine the impact of severe diarrhea on antibiotic absorption, it is prudent to use IV antibiotics in clinically unstable patients **(AIII).**

Immune reconstitution inflammatory syndrome has not been described in association with treatment for typical bacterial enteric pathogens.

Preventing Recurrence

The pharmacologic approach to recurrent enteric infections is covered in the section on directed therapy for each bacterial species. As noted above, secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII)** and, in some circumstances, for those with recurrent shigellosis **(BIII)** or campylobacteriosis **(BIII).**

Special Considerations During Pregnancy

The diagnosis of bacterial enteric infection in pregnant people with HIV is the same as in people who are not pregnant and should be managed the same, with several considerations. **Based on their safety profile, expanded-spectrum cephalosporins or azithromycin should be the first-line therapy for bacterial enteric infections during pregnancy if antimicrobials are required, depending on the organism and the results of susceptibility testing (BIII).**[80] Arthropathy has been noted in the offspring of animals treated with quinolones during pregnancy. However, studies evaluating quinolone use in pregnant people did not find an increased risk of birth defects or musculoskeletal abnormalities.[81-83] Thus, quinolones can be used for bacterial enteric infections in pregnant people with HIV if indicated by susceptibility testing or failure of first-line therapy, as listed above with a shared medical decision-making decision model in discussion with the patient. **(BIII).** TMP-SMX use in the first trimester should be avoided, if possible, because of an association with an increased risk of birth defects, specifically neural tube, cardiovascular, and urinary tract defects **(BIII).**[84-86] However, a review of potential risks related to TMP-SMX use cites the low quality of current data and supports the use of TMP-SMX in pregnant people with HIV as clinically indicated.[87] Clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX if they are capable of becoming pregnant prior to pregnancy or as soon as possible in their first trimester **(BIII).**[84,85,88] Neonatal care providers should be informed if maternal sulfa therapy was used near delivery because of the theoretical increased risk of hyperbilirubinemia and kernicterus in the newborn. Because oral rifaximin and fidaxomicin are not absorbed systemically, these can be used in pregnancy as in nonpregnant individuals. However, pregnant people should have a shared medical decision with their providers and be made aware about the limited data about Fidaxomicin in pregnancy **(BIII).**

Vancomycin and metronidazole are two antimicrobials that have been utilized in the perinatal period in the United States. Intravenous vancomycin has been utilized as intrapartum prophylaxis in the penicillin allergic patient colonized with group B streptococcus,[89] and minimal absorption is expected with oral therapy. Although vancomycin for enteric disease is recommended for use only in its oral formulation, which is not absorbed in meaningful concentrations from the gastrointestinal tract,[90] it should be noted that with intravenous use, vancomycin readily crosses the placenta.[91] A

study of 10 infants evaluated after the second or third trimester for *in utero* exposure of maternal intravenous vancomycin therapy for serious staphylococcal infections found no hearing loss or renal toxicity attributed to vancomycin.[91] A review of metronidazole use in pregnancy for treatment of trichomoniasis or bacterial vaginosis found no increase in risk of birth defects.[92] Studies on the use of metronidazole for CDI in pregnancy were not found.

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Bartonellosis

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Epidemiology

Bartonella species cause infections that include cat scratch disease, retinitis, trench fever, relapsing bacteremia, culture-negative endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis.[1] The latter two manifestations occur almost exclusively in individuals who are immunocompromised. Thirty-seven species and three subspecies of *Bartonella* have been described and are officially recognized (see Bartonella on the List of Prokaryotic Names with Standing in Nomenclature); fourteen of these *Bartonella* species have been implicated in human infections.

BA most often occurs late in HIV infection[2] in patients with median CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3. In people with HIV, bartonellosis is often a chronic illness, lasting for months to more than a year, with BA lesions and intermittent bacteremia. Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in people with HIV.[2] In contrast, BA caused by *B. quintana* is associated with body louse infestation and homelessness.[2] The body louse serves as the vector of *B. quintana* to humans. To avoid exposure to *B. quintana*, people with HIV should avoid body lice exposure and have prompt eradication of lice if infestation occurs. The cat flea is the vector of *B. henselae* in cats. Cats are the most common vector (via a scratch) responsible for transmitting *B. henselae* to humans, most likely when their claws become contaminated with feces from *B. henselae*-infected fleas. In some areas of the United States, the prevalence of *B. henselae* bacteremia in pet cats approaches 50%;[3] infection is more common among kittens and feral cat populations. Controlling cat flea infestation and avoiding cat scratches are therefore critical strategies for preventing *B. henselae* infections in people with HIV.

Clinical Manifestations

BA lesions have been associated with nearly every organ system, but cutaneous lesions are the most readily identified. These lesions can be clinically indistinguishable from Kaposi sarcoma, pyogenic granuloma, and other skin conditions. BA also can cause subcutaneous nodules. Osteomyelitis is usually caused by *B. quintana*, and only *B. henselae* causes bacillary peliosis hepatis.[2] Although isolated organs can appear to be the principal focus of disease, BA represents a hematogenously disseminated infection, and systemic symptoms of fever, night sweats, and weight loss often accompany BA. *Bartonella* infection is a major cause of unexplained fever in patients with advanced HIV and should be considered in the differential diagnosis of patients with CD4 counts <100 cells/mm^3 and fever.[4] *Bartonella* is a frequent cause of culture-negative endocarditis in immunocompetent and immunocompromised humans and is most commonly caused by *B. quintana*, less frequently by *B. henselae*, and rarely by other *Bartonella* species.[5] Immune complex disease (such as glomerulonephritis) may complicate endocarditis or other systemic *Bartonella* infections; assessment for immune complex formation may be warranted in such cases so that nephrotoxic agents can be avoided.

Diagnosis

Diagnosis of BA can be confirmed by histopathologic examination of biopsied tissue.[6] BA lesions are characterized by vascular proliferation, and a modified silver stain (such as Warthin-Starry stain) usually demonstrates numerous bacilli. Tissue Gram staining and acid-fast staining are negative.

A well-characterized indirect fluorescent antibody (IFA) serologic test was developed at the Centers for Disease Control and Prevention (CDC)[7] and is available at the CDC Infectious Diseases Laboratories. In addition, several private laboratories offer IFA serological testing, but the performance characteristics of these tests have not been validated for people with HIV. In immunocompetent patients, anti-*Bartonella* antibodies might not be detectable for 6 weeks after acute infection; in contrast, by the time *Bartonella* infection is suspected in patients with late-stage HIV infection, they usually have been infected with *Bartonella* for months or even >1 year. However, as many as 25% of *Bartonella* culture-positive patients never develop antibodies in the setting of advanced HIV infection.[4] In those patients who do develop anti-*Bartonella* antibodies, monitoring of antibody levels can be useful in following treatment response of *Bartonella* infection to antibiotics, reflecting resolution[8] or recrudescence. Because of interlaboratory variability, longitudinal testing should be conducted at the same laboratory to enable direct comparison of titers over time.

Because of their fastidious nature, *Bartonella* organisms can be isolated only with difficulty from blood (drawn into ethylenediaminetetraacetic acid [EDTA] tubes, centrifuged, and then plated directly onto fresh chocolate agar). *Bartonella* has been cultured directly from tissue in only a few laboratories.[2] Removing samples from blood culture bottles after 8 days of incubation, followed by staining with acridine orange, has facilitated identification and subsequent culture of *Bartonella* species.[9] Additionally, the CDC can perform polymerase chain reaction (PCR) amplification with universal and/or specific primers to detect *Bartonella* in EDTA blood samples (see *Bartonella quintana* Molecular Detection); these molecular detection tests also are increasingly available through private laboratories. Finally, molecular detection of *Bartonella* in BA skin lesions or other vascular lesions, lymph nodes, or resected cardiac valves from unfixed tissue biopsy samples (at the University of Washington) or from formalin-fixed tissue (at the CDC Infectious Disease Pathology Branch) can be performed.[8,10] *Bartonella* species may also be detected from blood or plasma using metagenomic next generation sequencing.[11-13] Clinicians should be aware that results from the CDC may take longer—several weeks to months—for serologic and molecular testing, respectively, compared with some private laboratories. A notable update was published in the 2023 Duke-ISCVID Criteria for Infective Endocarditis, indicating that an IFA immunoglobulin G (IgG) titer of ≥1:800 for *B. quintana* or *B. henselae* or identification of a *Bartonella sp.* by PCR or other nucleic acid–based techniques (including metagenomic sequencing) from blood are now considered major criteria for the diagnosis of *Bartonella* endocarditis.[14]

In summary, diagnosis of bartonellosis may require multiple testing modalities, including serologic testing (which is the most accessible test, and when positive, is helpful both for diagnosis and subsequent monitoring of treatment response), histopathology, and, especially, molecular testing for biopsied or resected tissue (e.g., BA lesion tissue or heart valve tissue).

Preventing Exposure

People with HIV, specifically those who are severely immunocompromised (CD4 counts <100 cells/mm^3), are at high risk of severe disease when infected by *B. quintana* or *B. henselae*. The

major risk factors for acquisition of *B. henselae* are contact with cats infested with fleas and receiving cat scratches. Immunocompromised individuals should consider the potential risks of cat ownership **(AIII).** People with HIV who want cats should acquire animals that are older than 1 year of age and in good health **(BII).** Cats should be acquired from a known environment, have a documented health history, and be free of fleas. Stray cats and cats with flea infestation should be avoided. Declawing is not advised, but individuals with HIV should avoid rough play with cats and situations in which scratches are likely **(AII).** People with HIV should avoid contact with flea feces (i.e., flea dirt), and any cat-associated wound should be washed promptly with soap and water **(BIII).** Care of cats should include a comprehensive, ongoing flea-control program under the supervision of a veterinarian **(BIII).** No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for *Bartonella* infection or from antibiotic treatment of healthy, serologically positive cats **(BII).** The major risk factor for *B. quintana* infection is body lice infestation. People with HIV who are experiencing homelessness or are in marginal housing should be informed that body louse infestation can be associated with serious illness and should be provided with appropriate measures to eradicate body lice, if present **(AII).** Regardless of CD4 count, people with both HIV and solid organ transplantation may be at risk of developing more severe *Bartonella* infections, similar to transplant recipients without HIV.[15]

Preventing Disease

Primary chemoprophylaxis for *Bartonella*-associated disease is not recommended **(BIII).** However, note that in a retrospective case-control study, use of a macrolide (such as for *Mycobacterium avium* complex prophylaxis) was protective against developing *Bartonella* infection.[2]

Treating Disease

Recommendations for Treating *Bartonella* Infections
Preferred Therapy
For Cat Scratch Disease, Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis
o Doxycycline 100 mg PO or IV every 12 hours **(AII)**, *or*
o Erythromycin 500 mg PO or IV every 6 hours **(AII)**
For Infections Involving the CNS
o Doxycycline 100 mg PO or IV every 12 hours +/– rifampin 300 mg PO or IV every 12 hours **(AIII)**
For Confirmed Bartonella Endocarditis
o (Doxycycline 100 mg IV every 12 hours + rifampin 300 mg IV or PO every 12 hours) for 6 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months **(BII)**, *or*
For Other Severe Infections (Multifocal Disease or with Clinical Decompensation)
o Doxycycline 100 mg PO or IV every 12 hours + rifampin 300 mg PO or IV every 12 hours **(BIII)**, *or*
o Erythromycin 500 mg PO or IV every 6 hours + rifampin 300 mg PO or IV every 12 hours **(BIII)**
Note: IV therapy may be needed initially **(AIII).**
Alternative Therapy
For Confirmed Bartonella Endocarditis

- o (Doxycycline 100 mg IV every 12 hours + gentamicin 1 mg/kg IV every 8 hours) for 2 weeks, then continue with doxycycline 100 mg IV or PO **every 12 hours for ≥3** months **(BII)**

For Bartonella Infections Other than Endocarditis or CNS Infections

- Azithromycin 500 mg PO daily **(BIII)**, *or*

- Clarithromycin 500 mg PO twice daily **(BIII)**

Duration of Therapy

- At least 3 months for all manifestations of *Bartonella* infection in patients with HIV

Long-Term Suppressive Therapy

Indication for Long-Term Suppressive Therapy

If a relapse occurs after a ≥3-month course of primary treatment:

- A macrolide or doxycycline as long as the CD4 count remains <200 cells/mm3 **(AIII)**

Indications for Discontinuing Long-Term Suppressive Therapy (CIII)

- Received at least 3–4 months of treatment, *and*

- CD4 count >200 cells/mm3 for at least 6 months

- Some specialists would discontinue therapy only if *Bartonella* titers have also decreased by 4-fold **(CIII)**.

Other Considerations

- Rifamycin class antibiotics are potent hepatic enzyme inducers and may lead to significant interaction with many drugs, including ARV agents (see the Dosing Recommendations for Anti-TB Drugs table in the [Mycobacterium tuberculosis Infection and Disease section](#) for dosing recommendations).

- In pregnancy, erythromycin or an alternative macrolide should be used as first-line therapy **(AIII)** rather than tetracyclines (such as doxycycline) due to toxicity profile; third-generation cephalosporins may have efficacy but are second line. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* **(AII)**.

Key: +/− = with or without; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CNS = central nervous system; IV = intravenously; PO = orally

All patients with HIV and *Bartonella* infection should receive antibiotic treatment **(AII).** No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in patients with HIV. Erythromycin and doxycycline have been used successfully to treat BA, peliosis hepatis, bacteremia, and osteomyelitis; either drug is considered first-line treatment for bartonellosis on the basis of reported experience in case series **(AII).**[1,2] Anecdotal and limited published case reports[16] suggest that other macrolide antibiotics (such as azithromycin or clarithromycin) are effective in treating *Bartonella* infections in patients with HIV and may be better tolerated than erythromycin; either of these can be an alternative therapy for *Bartonella* infections (except for endocarditis or central nervous system [CNS] infections) **(BIII).** Therapy should be administered for at least 3 months **(AII).** Doxycycline, preferably in combination with a rifamycin class antibiotic, is the treatment of choice for bartonellosis infection involving the CNS **(AIII).** For severe *Bartonella* infections (i.e., patients with multifocal disease or evidence of clinical decompensation), combination therapy using erythromycin or doxycycline with a rifamycin class antibiotic is recommended **(BIII);** intravenous therapy may be needed initially **(AIII).** Treatment of *Bartonella* endocarditis should include doxycycline with the addition of a rifamycin class antibiotic for a minimum of 6 weeks **(BII).** Doxycycline for 6 weeks plus gentamicin for the first 2 weeks may also be considered but is less

preferred due to the intrinsic nephrotoxicity of gentamicin and the frequency of vasculitis-induced renal dysfunction complicating *Bartonella* endocarditis **(BII).**[17]

Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis **(AII).**[18] *Bartonella* species have been isolated from patients with HIV during documented treatment or prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX);[2] quinolones and TMP-SMX also have variable *in vitro* activity and an inconsistent clinical response in case reports and are not recommended **(AIII).**

Monitoring of Response to Therapy and Adverse Effects (Including IRIS)

The potential exists for immune reconstitution inflammatory syndrome (IRIS) in association with bartonellosis treatment and initiation of antiretroviral therapy (ART) in people with HIV. In ART-naive patients, ART generally can be initiated at the same time as *Bartonella*-directed treatment; however, patients with *Bartonella* CNS or ophthalmic lesions probably should be treated with doxycycline and a rifamycin class antibiotic for 2 to 4 weeks before instituting ART **(CIII).**

Because of the propensity for relapse of *Bartonella* infection, patients should have anti-*Bartonella* IFA IgG antibody titers checked at the time of diagnosis (Note: It is important to specify to the receiving lab that the sample must be diluted to endpoint.) and, if positive, should be followed with sequential endpoint titers every 6 to 8 weeks during treatment, preferably until at least a fourfold decrease is documented **(CIII).**[8] Patients treated with oral doxycycline should be cautioned about pill-associated esophagitis and photosensitivity. Adverse effects associated with macrolides include nausea, vomiting, abdominal pain, and elevations of liver transaminase levels; potential QT interval prolongation also should be considered. Serious side effects can occur during treatment with rifamycin class antibiotics, including hypersensitivity reactions (thrombocytopenia, interstitial nephritis, and hemolytic anemia) and hepatitis. Administration of rifamycin class antibiotics strongly induces the cytochrome P450 enzyme system, which is an important consideration when other medications, including many antiretroviral drugs, are taken simultaneously.

Managing Treatment Failure

Relapse of *Bartonella* infections occurs frequently, especially in patients with BA. Among patients who fail to respond to initial treatment, switching to a different preferred regimen (for example, from doxycycline to erythromycin) may be considered, again with treatment duration of ≥3 months **(AIII).** For severe infections, the addition of a rifamycin class antibiotic is indicated **(AIII).** For patients with positive or increasing antibody titers, but with clinical improvement, treatment should continue until at least a fourfold decrease in the antibody titers is documented **(CIII).**[8]

Preventing Recurrence

After a primary course of treatment (minimum of 3 months), treatment may be discontinued, with close monitoring for evidence of relapse (e.g., symptoms, increase in antibody titers).

If a relapse occurs, an additional course of treatment is recommended, followed by long-term suppression of infection with doxycycline or a macrolide **(AIII).**

Long-term suppression can be discontinued after the patient has received at least 3 to 4 months of therapy and when the CD4 count remains >200 cells/mm^3 on effective ART for ≥6 months **(CIII).**[8]

Some specialists would discontinue therapy only if the *Bartonella* titers also have decreased at least fourfold **(CIII).**

Special Considerations During Pregnancy

Infection with *B. bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk of death, but no data are available on the effect of *B. quintana* or *B. henselae* infection during pregnancy.

The approach to diagnosis of *Bartonella* infections in pregnant people is the same as in nonpregnant people. Erythromycin treatment (or an alternative macrolide) should be used as first-line therapy **(AIII)** rather than tetracyclines (such as doxycycline) during pregnancy because of the increased risk of hepatotoxicity and the accumulation of tetracycline in fetal teeth and bones, resulting in dark, permanent staining of fetal teeth. Third-generation cephalosporins, such as ceftizoxime[19] or ceftriaxone, may have efficacy against *Bartonella* in pregnant people with HIV, but it should be considered second-line therapy after a macrolide. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* **(AII).**

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Candidiasis (Mucocutaneous)

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Epidemiology

Oropharyngeal and esophageal candidiasis are common in people with HIV.[1] The vast majority of such infections are caused by *Candida albicans,* although infections caused by non–*C. albicans* species have been increasingly reported worldwide, in part due to increased selection pressure from increased use of azoles.[2-9] The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression and is most often observed in people with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3, with esophageal disease typically occurring at lower CD4 counts than oropharyngeal disease.[10,11] In contrast, vulvovaginal candidiasis—whether a single episode or recurrent—is common in healthy adults and does not suggest HIV.

Clinical Manifestations

Oropharyngeal candidiasis (oral thrush) is characterized by painless, creamy white, plaque-like lesions that can occur on the buccal surface, hard or soft palate, gums, oropharynx, or tongue surface. In many cases, lesions can be scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular cheilosis also can be caused by *Candida*. Because a proportion of people with HIV who have oropharyngeal candidiasis also manifest esophageal involvement, clinicians should ascertain whether there are symptoms suggestive of esophageal disease in people with oropharyngeal candidiasis.

Esophageal candidiasis generally presents with retrosternal burning pain or discomfort along with odynophagia; occasionally, esophageal candidiasis can be asymptomatic. Endoscopic examination reveals whitish plaques similar to those observed with oropharyngeal disease. On occasion, the plaques may progress to superficial ulcerations of the esophageal mucosa with central or peripheral whitish exudates.

In contrast to oropharyngeal candidiasis, vulvovaginal candidiasis is less common in people with HIV and when it occurs, it is uncommonly refractory to azole therapy unless caused by non-*C. albicans* species. In people with HIV, *Candida* vulvovaginitis usually presents with white adherent vaginal discharge associated with mucosal burning and itching of mild-to-moderate severity and sporadic recurrences. In those with advanced immunosuppression, episodes may be more severe and recur more frequently.

Diagnosis

Oropharyngeal candidiasis is usually diagnosed clinically based on the characteristic appearance of lesions. In contrast to oral hairy leukoplakia, the white plaques of oropharyngeal candidiasis can be scraped off the mucosa. If laboratory confirmation is required, scrapings can be examined microscopically for characteristic yeast or hyphal forms, using a potassium hydroxide preparation. Cultures of clinical exudative material yield the species of *Candida* present.

Esophageal candidiasis should be suspected in people with low CD4 count with substernal chest pain, dysphagia, and odynophagia, especially if there is oral thrush present (though the absence of oral thrush does not rule out esophageal involvement). The diagnosis of esophageal candidiasis is often made empirically based on symptoms plus response to therapy. The definitive diagnosis of esophageal candidiasis requires direct endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and confirmation by fungal culture and speciation.

Vulvovaginal candidiasis usually is diagnosed based on clinical presentation coupled with the demonstration of characteristic blastosphere and hyphal yeast forms in vaginal secretions when examined microscopically after potassium hydroxide preparation. Culture confirmation is rarely required but may provide supportive information. Self-diagnosis of vulvovaginitis is unreliable; microscopic and culture confirmation is required to avoid unnecessary exposure to treatment and to assess for other potential pathogens including those that cause sexually transmitted infections (STIs).

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals. No measures are available to reduce exposure to these fungi.

Preventing Disease

Routine primary prophylaxis **is not recommended** because mucosal disease is associated with very low attributable morbidity and mortality and, moreover, acute therapy is highly effective.[12,13] Primary antifungal prophylaxis can lead to infections caused by drug-resistant *Candida* strains and introduce significant drug–drug interactions and QTc (QT corrected for heart rate) prolongation. In addition, long-term oral prophylaxis is expensive. Therefore, routine primary prophylaxis **is not recommended (AIII).** Administration of antiretroviral therapy (ART) and immune restoration is the most effective means to prevent disease.

Treating Disease

Treating Mucosal Candidiasis
Oropharyngeal Candidiasis: Initial Episodes (Duration of Therapy: 7–14 Days)
Preferred Therapy
• Fluconazole 200-mg loading dose, followed by 100–200 mg PO once daily **(AI)**
Alternative Therapy
• One 50-mg miconazole mucoadhesive buccal tablet once daily: Apply to mucosal surface over the canine fossa (do not swallow, chew, or crush tablet). Refer to the product label for more detailed application instructions. **(BI)**, *or*
• One 10-mg clotrimazole troche PO five times a day **(BI)**, *or*
• Nystatin suspension 4–6 mL PO four times daily **(BII)**, *or*
• Itraconazole oral solution 200 mg PO daily **(BI)**, *or*
• Posaconazole oral suspension 400 mg (10 mL) PO twice daily for 1 day, then 400 mg daily **(BI)**, *or*

- Posaconazole tablet 300 mg PO twice daily for 1 day, then 300 mg daily **(BI)**

Esophageal Candidiasis (Duration of Therapy: 14–21 Days)

Note: Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI)**; topical therapy alone is not recommended **(AI)**.

Preferred Therapy

- Fluconazole 200-mg loading dose, followed by 100–200 mg (up to 400 mg) PO or IV daily **(AI)**; consider oral suspension for people with severe symptoms and difficulty swallowing.

Alternative Therapy

- Itraconazole oral solution 200 mg PO daily **(AI)**, *or*
- Isavuconazole 400 mg PO as a loading dose, followed by isavuconazole 100 mg PO daily **(BI)**, *or*
- Isavuconazole 400 mg PO once weekly **(BI)**, *or*
- Voriconazole 200 mg PO or IV twice daily **(BI)**, *or*
- Posaconazole oral suspension 400 mg (10 mL) PO twice daily for 1 day, then 400 mg daily **(BI)**, *or*
- Posaconazole tablet 300 mg PO twice daily for 1 day, then 300 mg daily **(BI)**, *or*
- Lipid formulation of amphotericin B 3–4 mg/kg IV daily **(BI)**
- Caspofungin 70-mg loading dose IV, followed by 50 mg IV daily **(BI)**, *or*
- Micafungin 150 mg IV daily **(BI)**, *or*
- Anidulafungin 100 mg IV for one dose, then anidulafungin 50 mg IV daily **(BI)**

Note: A higher rate of esophageal candidiasis relapse has been reported with echinocandins than with fluconazole.

Uncomplicated Vulvovaginal Candidiasis

- Fluconazole 150 mg PO for one dose **(AII)**, *or*
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)**, *or*
- Ibrexafungerp 300 mg PO twice daily for 1 day **(BI)**, *or*
- For azole-refractory *Candida glabrata* vaginitis, boric acid 600 mg vaginal suppository once daily for 14 days **(BII)**

Severe or Recurrent Vulvovaginal Candidiasis

- Oral fluconazole (100–200 mg) PO daily or topical antifungals for ≥7 days **(AII)**
- *For recurrent only (the following regimens include treatment for the acute episode plus treatment to reduce incidence of recurrent episodes):*
  - Oteseconazole 600 mg PO at Day 1, 450 mg at Day 2, followed by once weekly 150 mg dosing starting at Day 14 for 11 weeks **(AI)** (for those who are not of reproductive potential); *or*
  - Fluconazole 150 mg PO at Days 1, 4, and 7, followed by oteseconazole 150 mg PO daily at Days 14 through 20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) **(AI)** (for those who are not of reproductive potential); or
  - Fluconazole 150 mg PO every 72 hours x 3 doses, followed by ibrexafungerp 300 mg PO twice daily 1 day per month for 6 months **(BI)** (use an effective form of contraception during treatment and for 4 days after the last dose)

Other Considerations
• Systemic azoles may have **significant** drug–drug interactions with ARV drugs (refer to <u>Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines</u>) and other drugs used for the treatment of opportunistic infections (refer to <u>Table 4: Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections</u>). Consider TDM if prolonged use is indicated.
• Fluconazole, itraconazole, posaconazole, and voriconazole can increase the risk for QTc prolongation, especially when co-administered with other QTc prolonging drugs that are cleared by CYP3A4.
• Chronic or prolonged use of azoles might promote development of resistance.

Considerations During Pregnancy and Lactation
• Topical therapy is preferable for treatment of oral candidiasis and vulvovaginal candidiasis in pregnancy. Oral fluconazole should be avoided when treating vulvovaginal candidiasis in the first trimester **(AIII)**.
• For pregnant people, substitution of amphotericin B for fluconazole in the first trimester is recommended for invasive or refractory esophageal *Candida* infections **(AIII)**.
• Human data are not available for micafungin, anidulafungin, caspofungin, thus their use in human pregnancy is not recommended **(AIII)**. Human data on the use of voriconazole are also not available, so its use is **not recommended**.
• Oteseconazole is **contraindicated** in pregnant and lactating individuals as animal studies have shown fetal malformations including ocular toxicity. Due to its long half-life, it is also contraindicated in females of reproductive potential despite the use of oral or other contraception.
• Ibrexafungerp is teratogenic in animal studies. Use in pregnant or lactating individuals is **contraindicated**.

Key: ARV = antiretroviral; CYP = cytochrome P450; IV = intravenous; PO = orally; QTc = QT corrected for heart rate; TDM = therapeutic drug monitoring

Oropharyngeal Candidiasis

Oral fluconazole is as effective as or superior to topical therapy for oropharyngeal candidiasis.[14] In addition, oral therapy is more convenient than topical therapy and usually better tolerated. Oral therapy has the additional benefit over topical regimens of being efficacious in treating esophageal candidiasis. Oral fluconazole at 100 to 200 mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy **(AI).**[14] One to 2 weeks of therapy until resolution of infection is recommended for oropharyngeal candidiasis.[14]

Using topical agents to treat oropharyngeal candidiasis includes several advantages: it reduces systemic drug exposure, diminishes the risk of drug–drug interactions and systemic adverse events, and may reduce the likelihood that antifungal resistance develops. As an alternative to oral fluconazole, once-daily miconazole in 50-mg mucoadhesive buccal tablets **(BI)** or five-times-per-day clotrimazole troches can be used to treat oropharyngeal candidiasis **(BI);** these regimens were shown to be equivalent in a multicenter, randomized study. Nystatin suspension four times daily remains an additional alternative **(BII).**[15] Unfavorable taste and multiple daily dosing, such as in the cases of clotrimazole and nystatin, may lead to decreased tolerability of and adherence to these topical therapies. If esophageal involvement is suspected, topical therapy alone is not recommended **(AI).**

Itraconazole is formulated as an oral solution or capsules, which differ in dosing and efficacy. Oral itraconazole for 7 to 14 days is as effective as oral fluconazole for oropharyngeal candidiasis but less well tolerated.[16] Posaconazole oral suspension[17] is also as effective as fluconazole and generally better tolerated than itraconazole solution, but it is more expensive. Although both posaconazole and

itraconazole have more drug–drug interactions than fluconazole, there are a few situations, such as *in vitro* resistance or poor clinical response, that would suggest these drugs be used in preference to fluconazole solely to treat mucosal candidiasis **(BI).** In a multicenter, randomized study, posaconazole was found to be more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued.[17] A oral delayed-release tablet formulation of posaconazole, which exhibits less variable absorption than the oral suspension, has been available.[18] Whether it offers any advantage for the treatment of oropharyngeal candidiasis has not been formally tested; however, it has been shown that switching from the oral suspension to the tablet formulation of posaconazole results in greater serum concentrations.[19] Itraconazole capsules are less effective than fluconazole because of their more variable absorption, and they are associated with more drug–drug interactions than fluconazole.

Esophageal Candidiasis

Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI).** A 14-day to 21-day course of either fluconazole (oral or intravenous [IV]) or oral itraconazole solution is highly effective and therefore recommended **(AI).** As with oropharyngeal candidiasis, however, itraconazole capsules for esophageal candidiasis may be less effective than fluconazole because of variable absorption Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis **(AI).** People with severe symptoms initially may have difficulty swallowing oral drugs; oral fluconazole suspension is available and should be considered in such patients. A 2-week course of isavuconazole, given orally at an initial loading dose of 400 mg followed by 100 mg once daily **(BI)** or 400 mg once weekly, is as effective as fluconazole for uncomplicated esophageal candidiasis and is recommended as an alternative regimen **(BI);** however, a higher rate of gastrointestinal adverse effects was seen with the 100-mg, once-daily isavuconazole regimen than with fluconazole and the other isavuconazole regimens.[20] Posaconazole, voriconazole, amphotericin B (lipid formulations), and the echinocandins caspofungin, micafungin, and anidulafungin all effectively treat esophageal candidiasis and also can be administered as alternatives **(BI);** however, esophageal candidiasis appears to have a higher relapse rate after treatment with the echinocandins.[21,22] Cost and insurance coverage also might be issues for the newer therapies.

Although infection with other pathogens that can cause esophagitis (e.g., cytomegalovirus, herpes simplex virus) can result in symptoms that mimic those of esophageal candidiasis, a diagnostic and therapeutic trial of antifungal therapy is usually warranted before endoscopy. In those who do not respond to antifungal therapy within 7 days, endoscopy is recommended to identify other potential causes of esophagitis or drug-resistant *Candida* **(AII).**

Vulvovaginal Candidiasis

In most people with HIV, vulvovaginal candidiasis is uncomplicated and responds readily to short-course oral or topical treatment with any of several therapies, including the following:

- Oral fluconazole **(AII)**

- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) **(AII)**

- Oral ibrexafungerp **(BI)**

Severe or recurrent episodes of vaginitis should be treated with oral fluconazole or topical antifungal therapy for ≥7 days **(AII).**

There are now additional options for recurrent vulvovaginal candidiasis that include treatment for the acute episode plus treatment to reduce incidence of recurrent episodes. One option for people who are not of reproductive potential is oteseconazole, a new tetrazole antifungal that was U.S. Food and Drug Administration (FDA)–approved in 2022. It exhibited efficacy when administered as 600 mg on Day 1 and 450 mg on Day 2, followed by once-weekly 150 mg dosing starting at Day 14 for 11 weeks or when it was administered after three fluconazole 150-mg doses administered at Days 1, 4, and 7, followed by oteseconazole 150 mg daily dosing at Days 14 through 20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4 through 14) **(AI).**[23,24]

Ibrexafungerp is an oral b-glucan synthase inhibitor that belongs in the class of triterpenoids. It was effective in Phase 2 and Phase 3 clinical trials of uncomplicated vulvovaginal candidiasis and was approved by the FDA in 2021.[25,26] In December 2022, ibrexafungerp was approved by the FDA for women with recurrent vulvovaginal candidiasis. Specifically, administration of fluconazole 150 mg every 72 hours for three doses, followed by ibrexafungerp 300 mg twice daily 1 day per month for 6 months was associated with absence of recurrent infection through week 24 in 65.4% of women compared to 53.1% of women who received placebo. These findings have been reported only in a press release,[27] with results available at ClinicalTrials.gov and on the FDA label,[28] and are thereby less compelling than peer-reviewed publication. Therefore, ibrexafungerp can be administered for recurrent vulvovaginal candidiasis **(BI).** Given the potential teratogenic effects of ibrexafungerp, treatment of women with recurrent vulvovaginal candidiasis who may become pregnant requires institution and documentation of effective contraception during treatment and for 4 days after the last dose.[29] For additional advice on managing Vulvovaginal Candidiasis, see the section in the STI Treatment Guidelines from the Centers for Disease Control and Prevention.

Special Considerations with Regard to Starting ART

There are no special considerations regarding initiation of ART in people with mucocutaneous candidiasis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for candidiasis has been completed. For information about drug–drug interactions between azoles and ARV agents, see the Drug–Drug Interactions section in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. For information about drug–drug interactions between azoles and other drugs used for the treatment of opportunistic infections, see Table 4: Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

For most people with mucocutaneous candidiasis, response to antifungal therapy is rapid; signs and symptoms improve within 48 to 72 hours. Short courses of topical therapy rarely result in adverse effects, although people may experience cutaneous hypersensitivity reactions characterized by rash and pruritus. Oral azole therapy can be associated with nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations. Liver function and the QTc interval should be monitored if azole therapy is anticipated for >21 days, especially in people with other hepatic comorbidities or on concomitant hepatotoxic drugs **(AII).** The echinocandins appear to be associated with very few adverse reactions: histamine-related infusion toxicity, transaminase elevations, and rash have been attributed to these drugs. No dose adjustments are required in renal failure.[30]

Immune reconstitution inflammatory syndrome (IRIS) with ART has rarely been reported for mucocutaneous candidiasis in people with HIV. Indeed, ART is associated with a markedly reduced incidence of candidiasis.[31,32]

Managing Treatment Failure

Antifungal treatment failure is typically defined as the persistence of signs or symptoms of oropharyngeal or esophageal candidiasis within 7 days of appropriate antifungal therapy. Refractory disease occurs in approximately 4% to 5% of people with HIV who have oral or esophageal candidiasis, typically those with CD4 counts <50 cells/mm^3 who have received multiple courses of azole antifungals.[4] Confirmatory culture with drug susceptibilities and, in the case of esophageal candidiasis, endoscopy, are necessary to assess for treatment failure due to azole resistance or other causes of esophagitis, especially if these procedures were not initially performed.

Posaconazole immediate-release oral suspension (400 mg twice daily for 28 days) is effective in 75% of people with azole-refractory oropharyngeal or esophageal candidiasis and is therefore recommended **(AI).**[33] Again, although the delayed-release tablet formulation of posaconazole is now available, it is not known whether it offers an advantage over the suspension for treating this particular disease. Alternatively, oral itraconazole solution is effective, at least transiently, in approximately two-thirds of people with fluconazole-refractory mucosal candidiasis and can be used as alternative therapy **(BII).**[16] If necessary, azole-refractory esophageal candidiasis also can be treated with anidulafungin **(BII),** caspofungin **(BII),** micafungin **(BII),** or voriconazole **(BII).**[21,22,34,35]

IV amphotericin B **(BII),** amphotericin B deoxycholate **(BII),** and the lipid preparations of amphotericin B **(BII)** are usually effective for treating azole-refractory disease and are therefore recommended. Amphotericin B oral suspension (1 mL of the 100-mg/mL suspension four times daily) can be administered to people with refractory oropharyngeal candidiasis who cannot take other oral options **(BII),** but this product is not commercially available in the United States and requires compounding by pharmacies.[36]

Patients with refractory vaginal candidiasis may benefit from intravaginal boric acid suppositories, which are commercially available at 600 mg.[37,38]

Preventing Recurrence

Preventing Recurrence
• Chronic suppressive therapy for recurrent oropharyngeal or vulvovaginal candidiasis is usually not recommended unless people have frequent or severe recurrences **(CIII)**.
• If used, it is reasonable to discontinue therapy if CD4 count increased to >200 cells/mm^3 following initiation of ART **(AIII)**.
If the Decision Is to Use Suppressive Therapy Because of Frequent or Severe Recurrences
Oropharyngeal Candidiasis
• Fluconazole 100 mg PO once daily or three times weekly **(BI)**
Esophageal Candidiasis
• Fluconazole 100–200 mg PO daily **(BI)**, *or*

- Posaconazole oral suspension 400 mg PO twice daily **(BII)**, *or*

- Posaconazole tablet 300 mg PO daily (**BII**)

Vulvovaginal Candidiasis

- Fluconazole 150 mg PO once weekly **(BII)** *or*

- Oteseconazole 600 mg at Day 1, 450 mg at Day 2 for treatment of the acute episode, followed by once-weekly 150-mg doses starting at Day 14 for 11 weeks **(AI)** (for those who are not of reproductive potential); *or*

- Fluconazole 150 mg at Days 1, 4, and 7 for treatment of the acute episode, followed by oteseconazole 150 mg daily at Days 14–20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) **(AI)** (for those who are not of reproductive potential); *or*

- Ibrexafungerp 300 mg twice daily 1 day per month for 6 months **(BI)** (use an effective form of contraception during treatment and for 4 days after the last dose.)

Considerations During Pregnancy and Lactation

- Chemoprophylaxis, either chronic maintenance therapy or secondary prophylaxis, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles should not be initiated during pregnancy **(AIII)**. Furthermore, prophylaxis with systemic azoles should be discontinued in people with HIV who become pregnant **(AIII)**.

- Oteseconazole is **contraindicated** in pregnant and lactating individuals as animal studies have shown fetal malformations including ocular toxicity. Due to its long half-life, it is also contraindicated in females of reproductive potential despite the use of oral or other contraception.

- Ibrexafungerp is teratogenic in animal studies. Use in pregnancy or during lactation is **contraindicated**.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally

When to Start Suppressive Therapy

A randomized clinical trial[39] of people with HIV who had CD4 counts <150 cells/mm^3 documented significantly fewer episodes of oropharyngeal candidiasis and other invasive fungal infections with continuous fluconazole therapy (three times a week) than with episodic fluconazole treatment for recurrences. This clinical trial also demonstrated no difference in the risk of developing clinically significant fluconazole resistance between the two fluconazole-treated groups among patients who were receiving ART.

However, secondary prophylaxis (chronic suppressive therapy) for recurrent oropharyngeal or vulvovaginal candidiasis **is not recommended** by most HIV specialists unless people have frequent or severe recurrences **(CIII)** because therapy for acute disease is effective, mortality associated with mucocutaneous disease is low, potential exists for drug interactions and for the development of antifungal-resistant *Candida*, and prophylaxis is costly.

If recurrences are frequent or severe, oral fluconazole can be used as suppressive therapy for oropharyngeal **(BI),** esophageal **(BI),** or vulvovaginal **(AII)** candidiasis.[40-42] Oral posaconazole twice daily is also effective for esophageal candidiasis **(BII).**[43] The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in people with HIV who are severely immunocompromised.[44] Several important factors should be considered when making the decision to use secondary prophylaxis. These factors include the effect of recurrences on the person's well-being and quality of life, the need for prophylaxis against other fungal infections, cost, adverse events, and, most importantly, drug–drug interactions.[45]

Rates of relapse are high in people with azole-refractory oropharyngeal or esophageal candidiasis who have initially responded to echinocandins, voriconazole, or posaconazole therapy. In such people, secondary prophylaxis should be instituted until immune reconstitution is achieved with the use of ART **(AIII).**

For information regarding oteseconazole and ibrexafungerp, see the Vulvovaginal Candidiasis Treatment Section above.

When to Stop Suppressive Therapy

In situations where secondary prophylaxis has been instituted, no data exist to guide recommendations regarding its discontinuation. Based on experience with other opportunistic infections, it would be reasonable to discontinue secondary prophylaxis when the CD4 count has increased to >200 cells/mm^3 following initiation of ART **(AIII).**

Special Considerations During Pregnancy

Pregnancy increases the risk of vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same in pregnant people as in those who are not pregnant.

Topical therapy is preferable for treatment of oral candidiasis and vulvovaginal candidiasis in pregnancy. Oral fluconazole should be avoided when treating vulvovaginal candidiasis in the first trimester **(AIII).** Data derived from women with vulvovaginal candidiasis suggest that fluconazole should not be used at any dose (including a single 150-mg dose) in the first trimester due to the risk of spontaneous abortion, while higher exposures (>150 mg dosing) during the first trimester are associated with cardiac septal closure defects.[46-50] A recent analysis of registry data from Sweden and Denmark did not find any increase in stillbirth or neonatal death associated with exposure to fluconazole at any dose during pregnancy.[51] Five cases of a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures (fluconazole embryopathy) have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.[48] A report from a national cohort register in Denmark found an increased hazard ratio (HR) of 1.48 for spontaneous pregnancy loss with any exposure to oral fluconazole from 7 to 22 weeks of pregnancy compared to unexposed, matched controls.[49] An increased HR of 1.47 was also noted with low-dose (150–300-mg cumulative dose) exposure. No increase in stillbirth was seen with fluconazole exposure broadly, but an increase in risk of stillbirth (HR, 4.10) was noted with fluconazole doses >300 mg.

Based on these data, substitution of amphotericin B for fluconazole in the first trimester is recommended for invasive or refractory esophageal *Candida* infections **(AIII).** Neonates born to those receiving chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Other azoles are similarly not recommended in pregnancy. Itraconazole at high doses has been shown to be teratogenic in animals,[52] but the metabolic mechanism accounting for these defects is not present in humans, so the data supporting this finding are of uncertain significance to human pregnancy. Case series in humans do not suggest an increased risk of birth defects with itraconazole,[53] but experience is limited. Human data are not available for posaconazole; however, the drug was associated with skeletal abnormalities in rats and was embryotoxic in rabbits when

given at doses that produced plasma levels equivalent to those seen in humans.[54] Evidence is inconclusive or inadequate for determining fetal risk associated with voriconazole use during pregnancy. An association with cleft palate and renal defects has been seen in rats, as well as embryotoxicity seen in rabbits.[55] Human data on the use of voriconazole are not available, so its use **is not recommended.** In animals, multiple anomalies have been seen with exposure to micafungin, and ossification defects have been seen with the use of anidulafungin and caspofungin.[56] Human data are not available for these drugs, thus their use in human pregnancy **is not recommended (AIII).**

The recently FDA-approved drugs for the treatment of vulvovaginal candidiasis, ibrexafungerp and oteseconazole, are **contraindicated** in pregnancy as animal studies have shown fetal malformations including ocular toxicity from oteseconazole.[29,57]

Chemoprophylaxis, either chronic maintenance therapy or secondary prophylaxis, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles **should not be initiated** during pregnancy **(AIII).** Furthermore, prophylaxis with systemic azoles **should be discontinued** in people with HIV who become pregnant **(AIII).**

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Chagas Disease

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Epidemiology

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*. It is transmitted to humans by infected triatomine bugs ("kissing bugs"), and less commonly by transfusion, organ transplant, from mother to infant, and, in rare instances, by ingestion of contaminated food or drink.[1-4]

Vector-borne transmission occurs only in the Americas, where an estimated 6 million people have Chagas disease.[5,6] Historically, transmission occurred largely in rural areas in Latin America, where houses built of mud brick are vulnerable to colonization by the triatomine vectors.[4] In such areas, Chagas disease usually is acquired in childhood. In the last several decades, successful vector control programs have substantially decreased transmission rates in much of Latin America.[4,7,8]

Infected triatomine vectors and *T. cruzi*–infected domestic and wild animals are found across the southern half of the United States, and rare cases of autochthonous vector-borne transmission have been documented.[9-11] However, the risk of vector-borne infection within the United States appears to be very low.[12] *T. cruzi* can also be transmitted in blood; screening of blood donations for anti-*T. cruzi* antibodies was introduced in 2007 after the U.S. Food and Drug Administration approved a serological test for that purpose.[13,14]

In people chronically infected with *T. cruzi* as a result of prior infection, profound immunosuppression (e.g., due to advanced HIV) may lead to reactivation of the disease, characterized by parasitemia, which is associated with increased intracellular parasite replication and lack of immunological control of the infection.[15-17]

Clinical Manifestations

Acute Phase. The acute phase of *T. cruzi* infection, which typically goes unrecognized, lasts up to 90 days and is characterized by circulating trypomastigotes detectable on microscopy of fresh blood or buffy coat smears.[2,4] If the portal of infection was the conjunctiva, patients may develop the characteristic Romaña's sign—unilateral painless swelling of the upper and lower eyelids—which usually lasts several weeks. The other symptoms of acute infection are usually limited to a non-specific febrile illness. In a small proportion of patients, however, acute, life-threatening myocarditis or meningoencephalitis may occur.[2,4] At the end of the acute phase, typically 60 to 90 days after infection, parasitemia falls below levels detectable by microscopy, and in the absence of effective antitrypanosomal treatment, *T. cruzi* infection passes into the chronic phase.[2,4]

Chronic Phase. Most patients with chronic *T. cruzi* infection have no signs or symptoms and are said to have the indeterminate form of the disease. Over the course of their lives, 20% to 30% of these patients will progress to clinically evident Chagas disease—most commonly, cardiomyopathy.[2,4] The earliest manifestations are usually conduction system abnormalities, such as right bundle branch block, alone or in combination with frequent premature ventricular contractions, which may develop years to decades after infection.[4,18] Over time, the disease may progress to

higher-grade heart block and complex ventricular arrhythmias. In patients with more advanced cardiomyopathy, poor prognostic factors include congestive heart failure, ventricular aneurysm, and complete heart block; these are associated with short-term mortality, including sudden death.[19] Chagas digestive disease is much less common than cardiomyopathy.[20] Dysphagia is the characteristic symptom of megaesophagus, and prolonged constipation is the most common complaint associated with megacolon.

T. cruzi reactivation during the chronic phase of Chagas disease is characterized by a return to high levels of parasite replication and parasitemia, which are usually detectable by microscopy. Reactivation can occur in individuals on immunosuppressive medications or cancer chemotherapy and in people with HIV.[16,21-25] Even in the absence of symptoms, people with HIV and chronic Chagas disease have significantly higher levels of *T. cruzi* parasitemia than their immunocompetent counterparts.[24] Most cases of clinically apparent reactivation occur with CD4 T lymphocyte cell counts <200 cells/mm^3, a history of prior opportunistic infections, or both.[16]

The clinical features of reactivated Chagas disease in people with HIV differ from those observed in individuals who are immunosuppressed for other reasons. The most common manifestations consist of *T. cruzi* meningoencephalitis, with or without brain abscesses (chagomas).[15,16,26,27] The presentation in people with HIV may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in people with HIV is acute myocarditis, sometimes superimposed on pre-existing chronic Chagas heart disease.[16,17] Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation, or rapid progression of existing chronic cardiomyopathy.[16,28] Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach, or intestine.[16,28]

Diagnosis

Screening with serological testing is recommended for all individuals who have lived in Mexico or Central or South America for greater than 6 months.[29]

Most persons infected with *T. cruzi* are in the chronic phase and are typically unaware of their infection. Screening for infection to identify persons with the indeterminate or early clinical forms of chronic Chagas disease is important to identify those who might benefit from antiparasitic treatment and counseling regarding potential transmission of *T. cruzi* to others (e.g., blood donation, organ donation). This is particularly important for people with HIV because of the risk of reactivation disease.

Diagnosis of chronic infection relies on serological methods to detect immunoglobulin G antibodies to *T. cruzi*, most commonly enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA). No available assay has sufficient sensitivity and specificity to be used alone; a single positive result does not constitute a confirmed diagnosis. Two serological tests based on different antigens (i.e., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA) should be used for individuals with suspected Chagas. In some cases, the infection status remains difficult to resolve even after a third test, because there is no true gold standard assay for chronic *T. cruzi* infection.[29,30]

Data suggest that the sensitivity of serological assays varies by geographical location, possibly because of *T. cruzi* strain differences and resulting antibody responses.[31,32] Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.[29,33] In general, polymerase chain reaction (PCR) is not a useful diagnostic test for chronic *T. cruzi* infection, as its sensitivity is highly variable.[30,34,35]

In people with HIV and epidemiologic risk factors for Chagas disease, coinfection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias or heart failure.[16,25,26] The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than *Toxoplasma* lesions.[17,26,27] Computed tomography and magnetic resonance imaging show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of *T. cruzi* amastigotes in glial cells and, less often, in neurons. Cerebrospinal fluid (CSF) typically shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes.[16,17,26,27] In a case series that included 15 people coinfected with HIV and *T. cruzi* with clinical meningoencephalitis, trypomastigotes were visualized in CSF in 85%.[36]

A definitive diagnosis of reactivation is established by identification of the parasite or its products in tissue, such as on brain biopsy, in CSF, or in blood.[16] In chronically infected patients who are immunocompetent or who have HIV coinfection in the absence of reactivation, trypomastigotes typically are undetectable in the circulating blood.[24] If observed in a coinfected patient, circulating parasites suggest reactivation and the need for treatment.

Testing to identify *T. cruzi* should be considered in all at-risk individuals with suspected reactivation of chronic Chagas disease. Initial assessment can be done by evaluation of a peripheral blood smear. Blood concentration techniques, such as capillary centrifugation, can improve sensitivity.[34] In centrifuged blood, *T. cruzi* trypomastigotes are found just above the buffy coat. Parasites also may be observed in lymph nodes, bone marrow, skin lesions, or pericardial fluid. Hemoculture is somewhat more sensitive than direct methods but takes 2 to 8 weeks to demonstrate parasites. Quantitative PCR assays performed on serial blood specimens that show rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation.[37,38] As such, clinicians should consider obtaining PCR testing in all individuals in whom there is high clinical suspicion and blood and/or tissue tests are negative.

In people with HIV who have suspected CNS Chagas disease, centrifugation and microscopic examination of CSF should be conducted. Few published data exist on PCR of CSF, but it would be expected to have high sensitivity for the diagnosis of reactivation in the CNS.[39]

In the United States, Chagas disease molecular detection (PCR testing for *T. cruzi* DNA) is available at the Centers for Disease Control and Prevention (CDC); consultations and testing requests should be addressed to Parasitic Diseases Hotline for Healthcare Providers (404-718-4745, parasites@cdc.gov, hours: 8 a.m.–4 p.m. ET/Monday–Friday) or through the CDC Emergency Operations Center (770-488-7100) for emergencies after business hours, on weekends, and federal holidays.

Preventing Exposure

Travelers to endemic countries may be at risk of infection with *T. cruzi* if they visit rural areas and stay in rustic lodging. The triatomine vector typically infests cracks in walls and roofing of poor-quality buildings that are constructed of adobe brick, mud, or thatch.[40] Because the insects feed at night, individuals who live in or visit Chagas disease–endemic areas should avoid sleeping in such dwellings or outdoors. Control programs in endemic areas rely on spraying infested dwellings with residual-action insecticide. If sleeping outdoors or in suspect dwellings cannot be avoided, sleeping under insecticide-treated bed nets provides significant protection.[41]

In the United States, all blood donors are screened for Chagas disease when they first donate blood. Universal screening of blood donors has been implemented in 21 Chagas disease–endemic Latin American countries.[42] Although transfusion-acquired cases have been uncommon in the United States, transfusion with infected blood products remains a risk for acquiring Chagas disease. No drugs or vaccines for preventing *T. cruzi* infection are available.

Preventing Disease

All people with HIV with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection.[29,43]

For people living with HIV, a single course of treatment with benznidazole or nifurtimox should be offered to individuals with *T. cruzi* infection who have not been previously treated and who do not have advanced Chagas cardiomyopathy, with a discussion of potential risks and benefits and shared decision making **(BIII).** However, the efficacy of currently available drugs in the chronic phase is suboptimal, there is no useful test of cure, and treated individuals are still considered at risk for reactivation.[32,44] There are no direct studies evaluating interactions between antiretroviral medications and either benznidazole or nifurtimox. However, as benznidazole may be partially metabolized by the cytochrome P450 (CYP) system, medications that inhibit this system may increase benznidazole toxicity and those that induce CYP enzymes may reduce benznidazole efficacy.[43,45]

Although direct data are lacking, optimization of antiretroviral therapy (ART) may help prevent Chagas reactivation in coinfected patients**.** Most symptomatic reactivation cases have occurred in people with HIV who were not virologically suppressed on ART.[16,43]

Treating Disease

Therapy for Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations or slowing progression in patients with acute and reactivated disease.[44,46] These drugs have limited efficacy, however, in achieving parasitological cure. As both drugs are U.S. Food and Drug Administration (FDA)–approved only for children, use for the treatment of adults in the United States is off-label. Individuals with advanced Chagas cardiomyopathy will not benefit from treatment. Consultation with a specialist should be sought. Consultations with experts at the CDC can be addressed to the Parasitic Diseases Hotline for Healthcare Providers (404-718-4745, parasites@cdc.gov).

Benznidazole (commercially available at http://www.benznidazoletablets.com/en) is approved by the FDA for use in children 2 to 12 years of age. The use of benznidazole to treat a patient outside of the

FDA-approved age range is based on clinical diagnosis and decision by a treating physician under practice of medicine. The regimen of 5 to 8 mg/kg/day in two divided doses taken with or without food for 60 days is the recommended treatment **(BIII);** a daily maximum dose of 300 mg is recommended by most experts.[47,48]

Nifurtimox (Lampit®) is also FDA approved for children less than 18 years of age and is available from retail sources.[49,50] Use of nifurtimox to treat a patient outside of the FDA-approved age range is based on clinical diagnosis and decision by the treating physician under practice of medicine. The recommended regimen is 8 to 10 mg/kg/day in three divided doses with food for 60 days **(BIII).**[51]

Treatment of patients outside of the FDA-approved age ranges for either drug is based on clinical diagnosis and decision by the treating physician under practice of medicine. The duration of therapy with either of these agents has not been studied in people with HIV. Mortality is high for symptomatic reactivated *T. cruzi* infection, even in patients who receive chemotherapy.[16,26] Limited data suggest that early recognition and treatment of reactivation may improve prognosis.[16]

Special Considerations with Regard to Starting Antiretroviral Therapy

As with other parasitic infections that localize in the CNS, the decision to initiate ART must be carefully considered in people with HIV and reactivated *T. cruzi* infection involving the brain. Only anecdotal information exists on the consequences of starting ART after a diagnosis of CNS Chagas disease, but there are no cases of Chagas-related immune reconstitution inflammatory syndrome (IRIS) that have been well described. Therefore, there is no known contraindication to starting or optimizing ART in patients with CNS Chagas disease. ART should be initiated in all patients with concomitant *T. cruzi* **(AIII).** In general, as IRIS is not recognized as a common manifestation in the setting of coinfection, treatment of *T. cruzi* does not warrant delay in ART.

Monitoring for Adverse Events

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are associated with significant toxicities.[46]

Benznidazole-associated adverse drug reactions include abdominal symptoms (abdominal pain, nausea, vomiting, diarrhea), reversible peripheral neuropathy, rash, and granulocytopenia. Comprehensive metabolic panel (CMP) and complete blood count (CBC) should be monitored before initiation and during therapy. Co-administration of benznidazole with disulfiram, alcohol, and products that contain propylene glycol should be avoided.

Nifurtimox-associated adverse drug reactions include anorexia, nausea, vomiting, abdominal pain and weight loss, rash, restlessness, tremors, and dose-dependent peripheral neuropathy. Alcohol consumption with nifurtimox should be avoided. CMP and CBC should be monitored before initiation and during treatment with nifurtimox.

The frequency of monitoring CMP and CBC during treatment, though not standardized, is generally every 2 weeks. The adverse effects of both drugs wane when the drugs are discontinued. For more information, refer to the Adverse Drug Reactions table.

As stated above, there are no reports at this time regarding *T. cruzi* infection and IRIS.

Managing Treatment Failure

People with HIV are at risk for clinical manifestations because of intermittent reactivation of chronic infection.[43] Benznidazole and nifurtimox are only partially effective in the chronic phase of *T. cruzi* infection and may be suppressive rather than curative.[44] Because the drugs are toxic and experience with their use in people with HIV is limited, expert advice should be sought.[46] Whether secondary prophylaxis or chronic maintenance therapy should be used in people with HIV with latent Chagas disease is unclear, particularly when potent ART is used.

There are no current recommendations for monitoring for reactivation after treatment. *T. cruzi* antibodies may persist after treatment. Reactivation after treatment is diagnosed based on compatible clinical symptoms and identification of the parasite in blood or CNS fluid/tissue by microscopy or PCR. Although no efficacy data are available, retreatment with benznidazole or nifurtimox is recommended for people with HIV and *T. cruzi* reactivation who fail to respond or who reactivate again after initial antitrypanosomal therapy **(AIII).**

Special Considerations During Pregnancy

As recommended for all individuals with epidemiologic risk of Chagas disease, screening of pregnant persons who have lived in endemic areas should be considered to identify maternal infection and possible risk of infection in their offspring. See the CDC resource for congenital Chagas disease for more information.

Between 1% to 10% of infants of mothers with *T. cruzi* are born with acute *T. cruzi* infection.[52] Most congenital *T. cruzi* infections are asymptomatic or cause non-specific signs; laboratory screening is required for detection of these cases.[53] In a small proportion of patients, congenital infection causes severe morbidity, including low birthweight, hepatosplenomegaly, anemia, meningoencephalitis, and/or respiratory insufficiency, with high risk of mortality.[52,54] Limited data suggest that the rate of congenital transmission is higher for women with HIV than in immunocompetent women.[16,55] Infants with HIV and concomitant *T. cruzi* also may be more likely to have symptoms, especially neurologic symptoms.[56,57]

Minimal data are available on the potential reproductive toxicity of benznidazole and nifurtimox, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease.[58,59] Benznidazole crosses the placenta in rats.[60] Due to the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection in pregnant people should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered only after completion of the pregnancy and breastfeeding. For pregnant people with HIV with symptomatic reactivation of *T. cruzi* infection, ART should be initiated **(AIII)** as initial treatment. Only two cases of treatment of Chagas disease in pregnancy with benznidazole have been reported in people with HIV.[61,62] One infant was born with a low birthweight.[62] All infants born to people with *T. cruzi* should undergo appropriate testing for congenitally acquired *T. cruzi* infection and be treated promptly if infection is confirmed.[63,64]

Recommendations for Preventing and Treating Chagas Disease (American Trypanosomiasis)

Preventing Manifestations of Chagas Disease

• All people with HIV who have epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* using at least two serological tests based on different antigens (e.g., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA).
 	
Indication
 	
• Individuals with epidemiological risk factors for Chagas disease who have tested positive for antibody to *T. cruzi*, have not been previously treated, and do not have advanced Chagas cardiomyopathy
 	
Therapy
 	
• A single course of benznidazole or nifurtimox is recommended by some experts (doses and duration same as for treatment of acute or reactivated infection).
 	
    o Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 60 days **(BIII)** (commercially available at http://www.benznidazoletablets.com/en). Most experts recommend a daily maximum of 300 mg.
 	
    o Nifurtimox (Lampit®) 8–10 mg/kg/day PO in 3 divided doses for 60 days **(BIII)** (commercially available through retail sources)
 	
Note: Efficacy of both therapies is suboptimal, and treated patients are still at risk of reactivation.

Treating Acute or Reactivated *T. cruzi* Infection
Indication   • Individuals with acute or reactivated *T. cruzi* infection as manifested by presence of parasitemia should be treated **(AII)**.   *Therapy*   • Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 60 days **(BIII)** (commercially available at http://www.benznidazoletablets.com/en). Most experts recommend a daily maximum of 300 mg.   • Nifurtimox (Lampit®) 8–10 mg/kg/day PO in 3 divided doses for 60 days **(BIII)** (commercially available through retail sources)   • Initiation or optimization of ART is recommended for all people with HIV with concomitant *T. cruzi* **(AIII)**.   **Note:** Treatment is not recommended for patients with advanced chagasic cardiomyopathy.

Key: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; ELISA = enzyme-linked immunosorbent assays; IFA = immunofluorescence assays; PO = orally

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Coccidioidomycosis

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Epidemiology

Coccidioidomycosis is caused by either of two soil-dwelling dimorphic fungi: *Coccidioides immitis* and *Coccidioides posadasii*. Most cases of coccidioidomycosis in people with HIV have been reported in the areas in which the disease is highly endemic.[1] Cases also may be identified outside of these areas when a person gives a history of having traveled through an endemic region. In the United States, the endemic areas include the lower San Joaquin Valley and other arid regions in California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas and Northern Mexico.[2] Several cases of coccidioidomycosis in individuals who acquired the infection in eastern Washington state have been reported and phylogenetically linked to local *Coccidioides immitis* isolates in nature.[2] These observations and others suggest that the coccidioidal endemic range may be expanding outside the traditional endemic range.

The risk of developing symptomatic coccidioidomycosis after infection is increased in people with HIV who have CD4 T lymphocyte (CD4) cell counts <250 cells/mm^3 and who are not virologically suppressed.[3,4] The incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[3,5]

Clinical Manifestations

Four common clinical syndromes of coccidioidomycosis have been described: focal pneumonia; diffuse pneumonia; extrathoracic involvement, including meningitis, osteoarticular infection, and other extrathoracic sites; and positive coccidioidal serology tests without evidence of localized infection.[6] In people with HIV, lack of viral suppression and CD4 count <250 cells/mm^3 are associated with increased severity of the presentation of coccidioidomycosis.[7]

Focal pneumonia is most common in people with CD4 counts ≥250 cells/mm^3. Focal pneumonia can be difficult to distinguish from bacterial or viral community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[7,8] However, symptoms such as hilar or mediastinal adenopathy, upper lobe infiltrates, nodules, peripheral blood eosinophilia, or rash—all of which are uncommon in bacterial pneumonia—may point towards coccidioidomycosis, particularly in patients who reside in, previously resided in, or have traveled to a known endemic area.

Diffuse pneumonia and extrathoracic disease usually occur in more apparently immunocompromised patients. Diffuse pulmonary disease presents with fever and dyspnea with a diffuse reticulonodular pattern on chest imaging, and in some instances may be difficult to distinguish clinically from *Pneumocystis* pneumonia.[9] Hypoxemia may be severe. Furthermore, serological tests may be negative at early presentation of infection.

Patients with meningitis present with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile in meningitis demonstrates low glucose levels, elevated protein levels, and a lymphocytic pleocytosis. Eosinophils may also be present on CSF analysis.

Elevated coccidioidal antibody titers even without symptoms can indicate risk of subsequent symptomatic diseases in people with HIV and advanced immunosuppression when CD4 count decreases to 10 cells/mm³ or less.[10]

Diagnosis

The diagnosis of coccidioidomycosis is based on serology, histology, culture, and clinical presentation. Culture of the organism from clinical specimens or by demonstration of typical spherules on histopathological examination of infected tissue—such as sputum, bronchoalveolar lavage fluid, joint aspirate, or tissue biopsy—proves the diagnosis. Positive blood cultures are rare and usually found only in those with diffuse pulmonary disease. CSF cultures are positive in fewer than one-third of patients with coccidioidal meningitis.

Unlike other endemic fungi, *Coccidioides* species grow relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a nonpigmented mold may be observed in as few as 3 to 7 days. *Coccidioides* growth on an agar plate is a significant laboratory biosafety hazard because of the risk of inhalation of dislodged arthroconidia. When a specimen is sent for culture, laboratory personnel should be alerted to the possibility of suspected coccidioidomycosis; in the laboratory, the culture plate lid should be kept secured with tape.[11] Identification of the fungus should be performed only in a biosafety level 3 or 2+ containment laboratory.

Most commonly, the diagnosis of coccidioidomycosis is based on a positive coccidioidal serological test and a compatible clinical syndrome. However, it may take several weeks for antibodies to develop in normal hosts and probably longer in immunocompromised hosts. Negative serology cannot be used to rule out disease, and therefore, tissue biopsy may be necessary. Repeat testing every 1 to 2 weeks should be considered if the patient is ill and the diagnosis has not been established.

On the other hand, patients with past coccidioidal infection and without disease activity usually revert to negative serological tests over 1 to 2 years. Thus, screening with an enzyme immunoassay (EIA) for immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody is recommended to detect the possibility of active disease. The EIA has a rapid turnaround time and is available in many clinical laboratories. These tests are very sensitive but occasionally have been associated with false positive results, particularly for IgM.[12] If either EIA test is positive, antibody assays by immunodiffusion (ID) and by complement fixation (CF) should be obtained to confirm the result and be used for further follow-up **(AI).** In cases of EIA positivity with negative ID, the clinical context needs to be carefully considered, as well as the value of further diagnostic workup. CF has been particularly useful in cerebrospinal fluid. A lateral flow assay has become available, but it is far less sensitive than EIA.[13]

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[14] serum,[15] and other body fluids, such as CSF,[16,17] in samples from individuals with active coccidioidomycosis.[18] The assay is most useful in diagnosing disseminated coccidioidomycosis. Detection of coccidioidal antigen in CSF has been reported to have a very high sensitivity and specificity for diagnosing coccidioidal meningitis, but assessing therapeutic responses with this method is more difficult.[19]

In addition, real-time polymerase chain reaction (RT-PCR) testing, if available, can be used on unfixed clinical specimens and on formalin-fixed tissue to aid in the diagnosis of

coccidioidomycosis. A *Coccidioides* RT-PCR assay is commercially available, but it has neither been U.S. Food and Drug Administration–approved nor tested in people with HIV.[20]

Preventing Exposure

People with HIV living in or visiting areas in which *Coccidioides* spp. are endemic cannot avoid exposure to the fungus. They should, however, avoid extensive exposure to disturbed native soil, such as at building excavation sites, without wearing proper N95 masks. Furthermore, in endemic areas, they should stay inside during dust storms **(BIII),** although the exact risk remains controversial.[21-23] However, no evidence indicates that gardening in cultivated soil in a coccidioidal endemic region increases the risk of acquiring coccidioidomycosis.

Preventing Disease

Preventing Coccidioidomycosis
Yearly or twice-yearly serological testing for coccidioidomycosis should be considered for serologically negative individuals with HIV who live in endemic areas **(BIII)**.
Primary antifungal prophylaxis or pre-emptive therapy **is not recommended** for individuals with HIV and low CD4 counts who live in endemic areas and who have negative serologic tests for *Coccidioides* **(AIII)**.
Indications for Primary Prophylaxis/Pre-Emptive Therapy **(AIII)**:   • Previously tested negative and with a new positive IgM or IgG test for *Coccidioides, and*   • No signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis, *and*   • CD4 count <250 cells/mm3
Preferred Therapy   • Fluconazole 400 mg PO once daily **(AIII)**
Discontinuation of Primary Prophylaxis/Pre-Emptive Therapy   • CD4 count ≥250 cells/mm3 with virologic suppression on ART **(BIII)**

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IgG = immunoglobulin G; IgM = immunoglobulin M; PO = orally

Primary antifungal prophylaxis (i.e., prophylaxis for individuals with negative results on serological tests for *Coccidioides*) does not appear to benefit people with HIV who have low CD4 counts and live in regions in which *Coccidioides* spp. are endemic,[5] and it **is not recommended (AIII).** Yearly or twice-yearly serological testing for coccidioidomycosis should be considered for serologically negative individuals with HIV who live in endemic areas **(BIII).** Testing is advised also for individuals who have previously traveled to or lived in endemic areas. Both IgM and IgG antibody testing using either an EIA or ID technique are recommended **(BIII).** In people who have CD4 counts <250 cells/mm^{3} and who previously tested negative for *Coccidioides*, a new positive serological test suggests possible active disease[10] and should prompt further clinical evaluation. If no signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis are identified, pre-emptive antifungal therapy with fluconazole 400 mg daily is recommended without definitive trials for those with a new positive serological test and CD4 counts <250 cells/mm^{3} **(AIII).** This regimen should be continued until the CD4 count is ≥250 cells/mm^{3} and virologic suppression is documented **(BIII).** For those with CD4 counts already ≥250 cells/mm^{3} and with viral suppression on

antiretrovirals (ARVs), close clinical follow-up without antifungal therapy is recommended **(BIII).** For asymptomatic patients who have not lived in or traveled to endemic regions, routine testing does not appear useful and **should not be performed (AIII).**

Treating Disease

Treating Coccidioidomycosis

Mild-to-Moderate Pulmonary Infections

Indications for Treatment

- Clinically mild infection, such as focal pneumonia

Preferred Therapy

- Fluconazole 400 mg PO once daily **(AII),** *or*

- Itraconazole 200 mg PO three times daily for 3 days then twice daily **(AII)**

Alternative Therapy (For Patients Who Failed to Respond to Fluconazole or Itraconazole)

- Voriconazole loading dose of 400 mg PO twice daily on Day 1, followed by 200 mg PO twice daily **(BIII),** *or*

- Posaconazole delayed-release tablet 300 mg PO twice daily on Day 1, followed by 300 mg once daily **(BIII),** *or*

- Isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO every 8 hours for six doses, followed by isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO once daily **(BIII)**

Severe Pulmonary or Extrapulmonary Infection (Except Meningitis)

Preferred Therapy

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII),** *or*

- Lipid formulation amphotericin B 3–5 mg/kg IV daily **(AIII),** particularly for those with underlying renal dysfunction

Use until clinical improvement, then switch to triazole (fluconazole 400 mg PO daily or itraconazole 200 mg PO twice daily) **(BIII).**

Alternative Therapy

- Some specialists recommend combining amphotericin B deoxycholate or lipid formulation amphotericin B (see above dosing) with a triazole (fluconazole or itraconazole 400 mg daily) as initial therapy and continue the triazole once amphotericin B is stopped **(CIII).**

Meningeal Infections (Consultation With a Specialist Is Advised [AIII])

Preferred Therapy

- Fluconazole 800–1,200 mg PO once daily **(AII)**

Alternative Therapy

- Itraconazole 200 mg PO two to three times daily **(BII),** *or*

- Voriconazole 200–400 mg PO twice daily **(BIII),** *or*

- Posaconazole delayed-release tablet 300 mg PO twice on Day 1, followed by 300 mg PO once daily **(CIII),** *or*

- Isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO every 8 hours for six doses, followed by isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO once daily **(CIII),** *or*

- Intrathecal amphotericin B deoxycholate **(AIII)** when triazole antifungals are not effective. Use in consultation with a specialist and ensure administration by a clinician experienced in this drug delivery technique.

Treatment in Pregnancy

Preferred Therapy During the First Trimester

- Lipid formulation amphotericin B 3–5 mg/kg IV daily **(AIII)**, *or*

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AIII)**

- **Note:** In general, azole antifungal agents should be avoided in the first trimester of pregnancy because of potential teratogenic effect unless benefit is thought to outweigh risk **(BIII)**.

- After the first trimester or when disease is diagnosed after the first trimester, treatment with fluconazole or itraconazole could be considered **(AIII)**.

Discontinuing Therapy

Focal Coccidioidal Pneumonia (AII)

- Discontinuation can be considered after the following:

  o Clinical response to 3–6 months of antifungal therapy, *and*

  o CD4 count ≥250 cells/mm^3, *and*

  o Virologic suppression on ART, *and*

- Continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis

- Relapse can occur in 25% to 33% of people without HIV and in people with HIV who have CD4 count ≥250 cells/mm^3.

- Discontinuation may be considered after ≥12 months of therapy based on clinical and serological response, and the decision should be made in consultation with experts **(BIII)**.

- For diffuse pulmonary disease, continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Coccidioidal Meningitis

- Relapse has been reported in 80% of patients after stopping triazoles; suppressive therapy at treatment doses should be lifelong. Discontinuation of therapy **is not recommended (AII)**.

Other Considerations

- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy. Use of corticosteroids **is not recommended**.

- All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines list these interactions and recommend dosage adjustments where feasible.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; CSF = cerebrospinal fluid; DDI = drug–drug interaction; IV = intravenous; PO = orally

Treatment of mild-to-moderate pulmonary coccidioidal infection: Therapy with an oral triazole antifungal agent is appropriate for patients who have clinically mild infection, such as focal pneumonia **(AII)**. Fluconazole should be given as 400 mg daily **(AII)**; itraconazole should be given in divided doses of 200 mg three times daily for 3 days, followed by 200 mg twice daily **(AII)**.[24,25]

Itraconazole is preferred for those who have bone or joint disease **(AI)**.[26] Serum itraconazole concentrations should be measured after the drug reaches steady state at 2 weeks to ensure adequate absorption. Target random serum concentrations (the sum of the parent itraconazole and hydroxyl itraconazole metabolite levels), measured by high-performance liquid chromatography, should be between 1.0 to 2.0 μg/mL.[27]

Data to support clinical efficacy for treatment with posaconazole,[28,29] voriconazole,[30] or isavuconazole[31] are limited, but these agents are recommended for patients who do not respond to fluconazole or itraconazole **(BIII)**. Voriconazole is given as a loading dose of 400 mg twice on Day 1, followed thereafter by 200 mg twice daily. Trough serum voriconazole concentrations should be measured to ensure efficacy and avoid toxicity; a concentration of 1 to 5 μg/mL is desired. Several dosage formulations of posaconazole have been studied for coccidioidomycosis. A dose of 400 mg twice daily of the older liquid formulation of posaconazole has been used,[29] but the current delayed-release tablet formulation of posaconazole at a dosage of 300 mg twice on the first day and then 300 mg once daily is better tolerated by people and provides more reliable serum concentrations and is therefore recommended **(BIII)**. A syndrome of mineralocorticoid excess manifesting as hypertension with hypokalemia was reported in some patients taking posaconazole.[32] Monitoring of blood pressure and serum potassium levels is appropriate in patients taking posaconazole.

Data supporting isavuconazole treatment in people with HIV are limited; however, in a cohort of 82 patients that included three people with HIV and CD4 ≥200 cells/mm³, improvement occurred in 70% of patients.[31] Isavuconazole is given as isavuconazole sulfate 372 mg (equivalent to isavuconazole 200 mg) every 8 hours for six doses then isavuconazole sulfate 372 mg (equivalent to isavuconazole 200 mg) once daily. Target serum isavuconazole levels are not always measured, but concentrations of 1 to 4.6 μg/mL are preferred, with adverse events increasingly common in concentrations exceeding 4.6 μg/mL.[33]

All triazole antifungals have the potential for complex and possibly bidirectional interactions with certain ARV agents and other anti-infective agents. The Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines and Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections list such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

Treatment of severe pulmonary coccidioidal infection or extrapulmonary infection:
Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or who are severely ill with extrathoracic disseminated disease **(AII)**.[25] Most experience has been with the deoxycholate formulation using a dose of amphotericin B of 0.7 to 1.0 mg/kg intravenously (IV) daily. There are only retrospective reports from studies that used lipid formulations of amphotericin B for the treatment of coccidioidomycosis.[34] Lipid formulations are likely to be as effective as the deoxycholate formulation and should be favored initial therapy, particularly in patients with underlying renal dysfunction **(AIII)**. For lipid formulations, a daily dose of amphotericin B of 3 to 5 mg/kg IV is appropriate. Therapy with amphotericin B should continue until clinical improvement is observed and then changed to an oral triazole antifungal **(BIII)**.

Some specialists recommend combining amphotericin B with a triazole antifungal (400 mg of fluconazole or itraconazole daily) at initiation of therapy, and then continuing the triazole once amphotericin B is stopped **(CIII)**.[25] No experience has been reported with single-dose liposomal amphotericin at 10 mg/kg combined with azoles as used in cryptococcosis.[35]

Treatment of patients with coccidioidal meningitis: Treatment of coccidioidal meningitis requires consultation with a specialist in the treatment of coccidioidal meningitis **(AIII).**[36] Intravenous amphotericin B alone is ineffective as treatment for coccidioidal meningitis. Treatment with a triazole antifungal is recommended instead with the early addition of the polyene. Fluconazole (800 to 1,200 mg daily) is the preferred regimen **(AII),**[24,37] but itraconazole 400 to 600 mg daily also has been successfully used **(BII).**[38] Therapy with voriconazole **(BIII),**[39-41] posaconazole **(CIII),**[29,42] and isavuconazole **(CIII)**[43] has been limited and described in individual case reports but has been successful and is generally used with expert opinions. Despite appropriate antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B deoxycholate is recommended **(AIII).**[44] When required, intrathecal therapy should be administered by someone very experienced in this drug delivery technique.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Monitoring the CF antibody titer is useful to assess response to therapy, which should be measured every 12 weeks. More than a twofold rise suggests recurrence or worsening of clinical disease and should prompt reassessment of management. Immune reconstitution inflammatory syndrome (IRIS) has been reported infrequently in people with HIV and coccidioidomycosis.[45-47] In general, delaying initiation of ART while treating coccidioidomycosis **may not be necessary (BIII).** However, in highly immunosuppressed patients (i.e., CD4 counts <100 cells/mm^3) with disseminated disease, clinical decline may occur with initiation of ART.[48] It might be prudent to delay ART for 4 to 6 weeks after initiating antifungal therapy in severely immunosuppressed patients who have disseminated or central nervous system (CNS) disease **(CIII).** On the other hand, ART delay may not always prevent IRIS, as reported in at least one patient with disseminated disease and who received treatment with fluconazole for 28 days but still had worsening symptoms within a week after starting ART.[49] Thus, close monitoring for clinical worsening, particularly if meningitis is present, is essential when treating highly immunosuppressed people who have HIV and disseminated coccidioidomycosis.

Managing Treatment Failure

Therapeutic random itraconazole concentrations of 1.0 μg/mL to 2.0 μg/mL should be the goal in patients with severe coccidioidomycosis who do not respond to treatment with itraconazole. In the case of confirmed treatment failure with adequate serum concentrations of the azole, treatment should be changed to IV amphotericin B, either deoxycholate or a lipid formulation for patients who are severely ill **(AIII).** For those who are not severely ill, posaconazole **(BIII),** voriconazole **(BIII),** or isavuconazole **(BIII)** are appropriate alternatives. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir- or cobicistat-boosted regimens (see the Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines). Posaconazole and voriconazole have known drug–drug interactions with ARVs.[50] In certain situations, surgical intervention may be indicated and is a bedside decision.[24]

Therapy After Immune Reconstitution

People with HIV and peripheral blood CD4 counts ≥250 cells/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[51] Moreover, a prospective study has demonstrated that coccidioidomycosis is less severe in those with lower HIV RNA and higher CD4 counts.[3] Given these facts, in people with HIV who have undetectable HIV RNA on potent ART and

who have CD4 count ≥250 cells/mm³, coccidioidomycosis should be managed no differently than it is in patients in the general population **(AII)**.

For patients with focal pulmonary disease who meet the above criteria, treatment with a triazole antifungal agent should continue for a minimum of 3 to 6 months **(AII)**. For patients with diffuse pulmonary disease or those with extrathoracic dissemination, antifungal therapy should continue for at least 12 months and usually much longer. Therapy should be discontinued based on clinical and immunological response and in consultation with an expert **(BIII)**. For people with detectable HIV viremia or CD4 count <250 cells/mm³, antifungal therapy at full dose should continue **(BIII)**.

Preventing Relapse

Relapse of coccidioidomycosis occurs in 25% to 33% of individuals without HIV who have diffuse pulmonary coccidioidomycosis or non-meningeal disseminated coccidioidomycosis[52,53] and may occur in people with HIV who have CD4 counts ≥250 cells/mm³ and are virologically suppressed on ARVs.[1,54] Patients with diffuse or focal coccidioidal pneumonia should have serial chest radiographs and coccidioidal serology tests every 3 to 6 months during coccidioidomycosis therapy and for 2 to 3 years after therapy discontinuation **(BIII)**. Relapses have been reported in ≥80% of patients with meningitis in whom triazoles have been discontinued.[55] Therefore, therapy for coccidioidal meningitis with treatment doses of the azole should be continued for life even in those with immune reconstitution **(AII)**.

Special Considerations During Pregnancy

Coccidioidomycosis should be considered in the differential diagnosis of a consistent clinical presentation in a pregnant person living in an endemic region or with an appropriate travel history. Reactivation during pregnancy in individuals with prior coccidioidomycosis but without active disease is uncommon, though the risk may be somewhat higher with a history of disseminated coccidioidomycosis.[56] When coccidioidomycosis is acquired later in pregnancy (e.g., during the second or third trimester) the infection is more likely to be more severe and potentially disseminated, with the greatest severity occurring during the immediate postpartum period.[56] There is no evidence that maternal coccidioidomycosis increases risk for pregnancy loss or premature delivery. Perinatal infection is uncommon and most likely acquired during delivery.[56]

Intravenous amphotericin B, formulated with deoxycholate or as a lipid preparation, is the preferred treatment for non-meningeal coccidioidomycosis during the first trimester of pregnancy **(AIII)**. Extensive clinical use of amphotericin B has not been associated with teratogenicity. There remain significant gaps in determining optimal dosing regimens in pregnancy; a recent review of dosing strategies in pregnancy recommended use of ideal body weight rather than total body weight to minimize risk of adverse effects to the fetus while maintaining efficacy.[57] Neonates born to women on chronic amphotericin B at delivery may be at increased risk for renal toxicity and electrolyte abnormalities and should be appropriately evaluated as newborns.[58]

For pregnant people with coccidioidal meningitis in the first trimester, for which the only alternative treatment to triazole antifungals is intrathecal amphotericin B, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the pregnant person, the infectious diseases consultant, and the obstetrician.[56]

In general, azole antifungals **should be avoided** during the first trimester of pregnancy unless the benefit is felt to outweigh the risk **(BIII).** Fluconazole has teratogenic potential in the first trimester. After the first trimester or when disease is diagnosed after the first trimester, treatment with fluconazole or itraconazole could be considered **(AIII).**[24] Congenital malformations, including craniofacial and limb abnormalities similar to those observed in animals exposed to fluconazole, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[56,59] Furthermore animal data suggest that moderate alcohol consumption during pregnancy may increase the potency of fluconazole resulting in increased risk of craniofacial defects.[60]

Most studies on the effects of fluconazole in pregnancy have involved low doses and short-term exposure. A meta-analysis of literature describing birth defects in infants exposed to fluconazole during the first trimester evaluated nine cohort, case-control or randomized controlled studies, including 53,407 fluconazole-exposed pregnant people and 3,319,353 unexposed pregnant people.[61] Maternal fluconazole use was correlated with an increased prevalence of heart defects in infants for both a low dose ($\leq$150 mg) (odds ratio [OR] 1.95; 95% confidence interval [CI], 1.18–3.21; $P = 0.01$) and any dose (OR 1.79; 95% CI, 1.18–2.71; $P = 0.01$). No association was found between fluconazole exposure and orofacial, CNS, genitourinary, musculoskeletal, or gastrointestinal defects at either low- or high-dose exposure to fluconazole. One registry-based cohort study of 7,352 women reported a threefold increase in incidence of Tetralogy of Fallot,[62] and a large population-based case-control study specifically noted an increase in transposition of the great arteries (OR 7.56; 95% CI, 1.22–35.45).[63] The latter study also suggested an increase in cleft lip with cleft palate (OR 5.53; 95% CI, 1.68–18.24). In three nested case-control studies using data from the Quebec Prescription Drug Insurance database, there was an increased prevalence of cardiac septal closure anomalies for maternal fluconazole doses greater than 150 mg during pregnancy (OR 1.81; 95% CI, 1.04–3.14).[64] A recent population-based cohort study (included in the meta-analysis) of 1,969,954 pregnancies, including 37,650 pregnancies exposed to fluconazole, found an increased risk of musculoskeletal malformations following exposure to fluconazole during the first trimester of pregnancy (risk of 52.1 per 10,000 pregnancies exposed to fluconazole versus 37.3 per 10,000 pregnancies exposed to topical azoles).[65]

A systematic review and meta-analysis of 6 cohort or case-control studies that analyzed more than 16,000 exposures and reported fetal outcomes after exposure to fluconazole used in the first trimester of pregnancy found a marginal association with increased risk of congenital malformations (OR 1.09; 95% CI, 0.99–1.2, $P = 0.088$), including heart defects, as well as spontaneous abortion; exposure to more than 150 mg was associated with an overall increase in congenital malformations.[61]

A nationwide cohort study in Denmark found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies (n = 16,561; hazard ratio [HR] 1.48; 95% CI, 1.23–1.77) or those with topical azole exposure only (n = 5,646; HR 1.62; 95% CI, 1.26–2.07).[66] Similarly, the nested case-control studies in Canada (n = 320,868 pregnancies) found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies and that risk was greater with higher dose of fluconazole exposure (adjusted OR for $\leq$150 mg fluconazole 2.23; 95% CI, 1.96–2.54; adjusted OR for >150 mg fluconazole 3.20; 95% CI, 2.73–3.75).[64] However, a cohort study using Swedish and Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use during pregnancy and risk of stillbirth or neonatal death.[67] The meta-analysis noted above also found no association between fluconazole exposure and risk of

abortion or stillbirth. On the basis of reported birth defects, the use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh the risks.

Although case reports of birth defects in infants exposed to itraconazole have occurred, a recent systematic review and meta-analysis of four cohort studies involving 971,450 pregnant women with 1,311 exposures found no significant difference in the overall risk of birth defects between those with maternal exposure to itraconazole and non-exposure.[68] Although limb and congenital heart defects were the most common defects seen, they were within the rates of these defects published by EUROCAT (the European network of population-based registries for epidemiological surveillance of congenital anomalies). However, the rate of eye defects was higher than that published by EUROCAT. No difference was found in rates of in spontaneous abortion or stillbirth based on itraconazole exposure. In sum, itraconazole should be used in pregnancy depending on a cost-benefit analysis.

Voriconazole (at doses lower than recommended human doses), posaconazole, and isavuconazole are teratogenic and embryotoxic in animal studies; no adequately controlled studies have assessed their teratogenicity and embryotoxicity in humans. Voriconazole, posaconazole, and isavuconazole **are not recommended** for use during pregnancy, especially in the first trimester **(AIII).**

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69.

Community-Acquired Pneumonia

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Epidemiology

Bacterial respiratory diseases, including sinusitis, bronchitis, otitis, and pneumonia, are among the most common infectious complications in people with HIV, occurring with increased frequency at all CD4 T lymphocyte cell (CD4) counts.[1] This chapter will focus on the diagnosis, prevention, and management of bacterial community-acquired pneumonia (CAP) in people with HIV. While viral pneumonias are a frequent cause of CAP, particularly influenza and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the management of coronavirus-19 (COVID-19) disease is outside the scope of these guidelines (refer to [NIH COVID-19 Treatment Guidelines](#) for updated treatment recommendations). These guidelines also do not consider hospital acquired pneumonia and ventilator-associated pneumonia; limited data suggest that these do not differ in terms of microbiology, clinical course, treatment, or prevention in people with HIV as compared to in people without HIV with similar HIV-unrelated comorbidities.

Bacterial pneumonia is a common cause of HIV-associated morbidity. Recurrent pneumonia, considered two or more episodes within a 1-year period, is an AIDS-defining condition. The incidence of bacterial pneumonia in individuals with HIV has decreased progressively with the advent of combination antiretroviral therapy (ART).[2-7] In one study, the incidence of bacterial pneumonia declined from 22.7 episodes per 100 person-years before the introduction of ART to 9.1 episodes per 100 person-years by 1997 after ART was introduced. Since then, the incidence of bacterial pneumonia among people with HIV in developed countries has continued to drop. In the Strategic Timing of AntiRetroviral Treatment (START) study, the incidence rate of serious bacterial infections overall was 0.87 per 100 person-years, and approximately 40% of these infections were due to bacterial pneumonia.[4] Recurrent bacterial pneumonia as an AIDS-defining illness is also less frequently encountered in individuals on ART; however, its exact incidence is hard to evaluate because surveillance data for it are not collected systematically as for other opportunistic infections (OIs).[8]

Risk Factors

Yet despite ART, bacterial pneumonia remains more common in people with HIV than in those who do not have HIV.[9-11] Bacterial pneumonia may be the first manifestation of underlying HIV infection and can occur at any stage of HIV disease and at any CD4 count. Bacterial pneumonia in individuals with HIV results from multiple risk factors, particularly immune defects. A CD4 count decrease, especially when below 100 cells/mm^3, continues to be a major risk factor for pneumonia due to routine bacterial pathogens. Other immune defects include quantitative and qualitative B-cell abnormalities that result in impaired pathogen-specific antibody production, abnormalities in neutrophil function or numbers, and abnormalities in alveolar macrophage function.[12,13] Lack of ART or intermittent use of ART increases the risk for pneumonia, likely due to uncontrolled HIV viremia.[14]

Additional risk factors that contribute to the continued risk for bacterial pneumonia in individuals with HIV include chronic viral hepatitis, tobacco, alcohol, injection drug use and prescribed opioid

use, particularly higher doses and opioids with immunosuppressive properties.[3,10,15,16,17] Chronic obstructive pulmonary disease (COPD), malignancy, renal insufficiency, and congestive heart failure (CHF) are emerging as risk factors for pneumonia, particularly in the population of older adults with HIV.[18] Risk for CAP can also increase with obesity[4], an emerging health problem in people living with HIV.

Microbiology

In individuals with HIV, *Streptococcus pneumoniae* (*S. pneumoniae)* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia, the same as in individuals without HIV.[19-25] *Staphylococcus aureus* (*S. aureus)* and *S. pneumoniae* are among the most common etiologies of pneumonia in association with influenza infection.[26,27] Atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila* species have been reported as infrequent causes of CAP in individuals with HIV.[22,28] However, when more extensive testing such as serology to detect IgM antibodies (IgM) antibodies and/or positive polymerase chain reaction (PCR) of respiratory secretions was performed, additional infections due to *Mycoplasma* and *Chlamydia* were detected.[29]

Additional microbial etiologies of CAP that should be considered in people with HIV include *Mycobacterium tuberculosis, Pneumocystis*, other opportunistic infections, and respiratory viruses. The incidence of these different organisms will vary depending on geographic region and patient risk factors including degree of immunocompromise when considering opportunistic infections. For example, in a recent prospective study from South Africa of 284 patients with HIV and suspected pneumonia, sputum real-time multiplex PCR testing found that tuberculosis was more common than bacterial causes of CAP in this setting; viruses were detected in 203 patients, with the most common being human metapneumovirus, although the pathogenic significance of the viral pathogens was uncertain.[30] As noted, respiratory viruses, influenza and SARS-CoV-2 are also common causes of CAP in people with HIV. While influenza and COVID-19 generally present similarly in people with and without HIV, some studies suggest mortality may be increased among people with HIV for these viral infections, particularly in low-and-middle income country settings.[31-36]

Risk Factors for Pseudomonas aeruginosa *and Methicillin-Resistant* Staphylococcus aureus

The frequency of *Pseudomonas aeruginosa* (*P. aeruginosa)* and *S. aureus* as community-acquired pathogens is higher in individuals with HIV than in those without HIV based on studies in the early combination ART era.[23,37] Many of these patients often had poorly controlled HIV or the presence of other concomitant risk factors that contributed to risk for *P. aeruginosa* or *S. aureus*. Patients with advanced HIV disease (CD4 count ≤50 cells/mm^3) or underlying neutropenia, as well as pre-existing lung disease such as bronchiectasis or severe COPD have an increased risk of infection with *P. aeruginosa*. Other risk factors for infection include the use of corticosteroids, severe malnutrition, hospitalization within the past 90 days, residence in a health care facility or nursing home, and chronic hemodialysis.[38]

S. aureus should be considered in patients with recent viral infection (particularly influenza), a history of injection drug use, or severe, bilateral, necrotizing pneumonia. Risk factors for *S. aureus* pneumonia in patients with HIV include receipt of antibiotics prior to hospital admission, comorbid illnesses, and recent healthcare contact.[39] Community outbreaks of methicillin-resistant *S. aureus* (MRSA) infection have also been seen among men who have sex with men.[40] Studies of patients

without HIV have identified hemodialysis, known prior colonization or infection with MRSA, as well as recurrent skin infections to be risk factors for MRSA pneumonia.[38] Notably, nasal carriage and colonization of skin sites with MRSA is more common in individuals with HIV than in those without HIV, and is more likely in patients recently incarcerated and/or hospitalized.[41,42]

Clinical Manifestations

Clinical and Radiographic Presentation

The clinical and radiographic presentation of bacterial pneumonia in individuals with HIV, particularly in those with higher CD4 count and HIV viral suppression, is similar to that in individuals without HIV.[43] Patients with pneumonia caused by bacteria such as *S. pneumoniae* or *Haemophilus* species characteristically have acute onset (3 to 5 days) of symptoms, including fevers, chills, rigors, chest pain or pleurisy, cough productive of purulent sputum, and dyspnea.[44] The presence of fever, tachycardia, and/or hypotension can be indicators of sepsis. Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia, and in such cases, clinicians should strongly consider hospitalizing the patient.

Patients with bacterial pneumonia typically have signs of focal consolidation, such as egophony, and/or pleural effusion on lung examination. In contrast, lung examination often is normal in those with *Pneumocystis* pneumonia (PCP), and if abnormal, reveals inspiratory crackles. In patients with bacterial pneumonia, the white blood cell (WBC) count usually is elevated. The elevation may be relative to baseline WBC count in those with advanced HIV. Neutrophilia or a left shift in WBC differential may be present.

Individuals with bacterial pneumonia characteristically exhibit unilateral, focal, segmental, or lobar consolidation on chest radiograph. The frequency of these typical radiographic findings, however, may depend on the underlying bacterial pathogen. Those with pneumonia due to *S. pneumoniae* or *Haemophilus* typically present with consolidation, whereas cavitation may be a feature more suggestive of *P. aeruginosa* or *S. aureus*.

Risk Factors for Bacteremia

In individuals with HIV the incidence of bacteremia accompanying pneumonia is greater than in individuals without HIV, especially when infection is due to *S. pneumoniae*.[45] In data from the CDC, the incidence of invasive pneumococcal disease, inclusive of bacteremia, was significantly higher in individuals with HIV: rates were 173 cases per 100,000 in those with HIV infection, compared to 3.8 per 100,000 in younger adults aged 18–34 years and 36.4 per 100,000 among those aged ≥65 years in the general population.[46] Similarly, in a study from Kenya, the rate of pneumococcal bacteremia was significantly higher in individuals with HIV infection (rate ratio of HIV-infected versus HIV-negative adults, 19.7, 95% CI 12.4-31.1).[47] With the introduction of ART and pneumococcal conjugate vaccines for both the general pediatric population and individuals living with HIV, this disparity in incidence rates of bacteremia between people with and without HIV has narrowed but has not been eliminated.[48-52] In one recent study of invasive pneumococcal disease (IPD), which includes bacteremia, IPD was more common in people with HIV who had CD4 counts < 500 cells/mm^3, but even those with counts > 500 cells/mm^3, had a higher incidence than in the general population.[53] Risk factors associated with bacteremia include lack of ART, low CD4 count (particularly <100 cells/mm^3), as well as alcohol abuse, current smoking, and comorbidities, particularly liver disease.[49]

Severity of Illness

Disease severity and arterial oxygenation should be assessed in all patients with pneumonia. Noninvasive measurement of arterial oxygen saturation by pulse oximetry is an appropriate screening test. Arterial blood gas analysis is indicated for patients with evidence of hypoxemia suggested by noninvasive assessment and for patients who have tachypnea and/or respiratory distress. Assessment of additional clinical features and the use of severity scoring systems for pneumonia such as the Pneumonia Severity Index (PSI) and CURB-65 and their application to patients with HIV are discussed in the Treating Disease section.

Outcomes

Although some studies suggest that bacterial pneumonia is associated with increased mortality in individuals with HIV,[23,54,55] others do not.[43,56-58] Independent predictors of increased mortality in a prospective, multicenter study of individuals with HIV with community-acquired bacterial pneumonia were CD4 count <100 cells/mm^3, radiographic progression of disease, and presence of shock.[59] In that study, multilobar infiltrates, cavitary infiltrates, and pleural effusion on baseline imaging were all independent predictors of radiographic progression of disease. However, in patients on ART with controlled HIV viremia, and high CD4 counts (>350 cells/mm^3), the clinical courses and outcomes of pneumonia appear to be similar to those in patients without HIV.[43]

As in patients without HIV, pneumonia may have an impact on longer term outcomes of patients with HIV. This includes greater long-term mortality, as hospitalization for pneumonia has been associated with increased mortality up to one year later.[60] One factor that may add to this long-term mortality is cardiovascular disease associated with CAP, which occurs at a similar rate in those with HIV infection , as those without, even though in one retrospective cohort study of 4,384 patients, people with HIV were younger, had less severe CAP and fewer traditional cardiovascular risk factors than those without HIV infection.[61] Pneumonia has also been associated with impaired lung function and risk of subsequent lung cancer in individuals with HIV.[62-64]

Diagnosis

General Approach

Patients with clinical symptoms and signs suggestive of CAP should have posteroanterior and lateral chest radiographs; evidence of pneumonia can also be found on chest computed tomography (CT) scan, but routine use of chest CT scan for this purpose is not recommended. Lung ultrasound can also be used to aid in the diagnosis pneumonia. If previous radiographs are available, they should be reviewed to assess for new findings. The clinical diagnosis of bacterial pneumonia requires a demonstrable infiltrate by chest radiograph or other imaging technique in conjunction with compatible clinical symptoms and signs.

The differential diagnosis of pneumonia in individuals with HIV is broad and a confirmed microbiologic diagnosis should be pursued. Microbial identification can allow clinicians to target the specific pathogen(s) and discontinue broad spectrum antibiotic therapy and/or empiric therapy that targets non-bacterial pathogens. Microbiologic testing should include evaluation of the upper respiratory tract for SARS-CoV-2, influenza in the appropriate season, and may include testing other respiratory viruses.[65] Given the increased incidence of *Mycobacterium tuberculosis* (*M. tuberculosis*) in individuals with HIV, a tuberculosis (TB) diagnosis should always be considered in patients with

HIV who have pneumonia, particularly in high incidence areas. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB (i.e., airborne precautions for hospitalized patients), and two to three sputum specimens should be obtained for acid fast bacilli evaluation (including TB PCR; see *Mycobacterium tuberculosis* Infection and Disease section). Bronchoscopy with bronchoalveolar lavage should be considered, especially if the differential diagnosis includes opportunistic pathogens such as *Pneumocystis jirovecii*.

Procalcitonin (PCT) testing has been proposed as a tool to distinguish between bacterial and viral respiratory infections. One study from Africa specifically evaluated the usefulness of PCT testing to distinguish CAP due to bacteria (non-TB), *M. tuberculosis*, and PCP in people with HIV. In general, PCT levels associated with bacterial pneumonia are higher than those associated with viral or fungal pneumonias, but levels can also be elevated in non-bacterial pulmonary infections.[66] Specific PCT thresholds have not been established or validated in HIV-associated bacterial pneumonia. Thus, given the lack of data, the use of PCT to guide decisions regarding etiology of pneumonia, initiation of anti-bacterial treatment, or duration of treatment in patients with HIV is not recommended.

Recommended Diagnostic Evaluation in CAP

American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) guidelines for microbiologic testing for diagnosis of CAP in individuals without HIV generally also apply to people with HIV.[67]

- In patients with HIV with CAP who are well enough to be treated as outpatients, routine diagnostic tests to identify a bacterial etiologic diagnosis are optional, especially if the microbiologic studies cannot be performed promptly.

- In patients with HIV hospitalized for CAP, a Gram stain of expectorated sputum and two blood cultures are recommended, particularly in those with severe pneumonia, in those who are not on ART; or in those who are known to have a CD4 count <350 cells/mm^3 (and especially if <100 cells/mm^3) prior to hospitalization. Specimens should ideally be obtained before initiation of antibiotics, or within 12 hours to 18 hours of such initiation.

- Urinary antigen tests for *L. pneumophila* and *S. pneumoniae* are recommended in hospitalized patients, particularly those with severe CAP. In addition, lower respiratory tract secretions should be cultured for *Legionella* on selective media or undergo *Legionella* nucleic acid amplification testing in adults with severe CAP. Legionella testing should also be done in people with HIV with non-severe CAP when indicated by epidemiological factors, such as association with a *Legionella* outbreak or recent travel.

- Microbiologic diagnostic testing is indicated whenever epidemiologic, clinical, or radiologic clues prompt suspicion of specific pathogens that could alter standard empirical management decisions.

- If available, rapid MRSA nasal testing should be performed, particularly in patients with risk factors for MRSA or in a high prevalence setting, as results can direct empiric antibiotic therapy.[68]

Gram stain and culture of sputum is recommended in all hospitalized patients meeting the criteria stated above, and is optional in people with HIV with CAP not meeting these criteria. In general, Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained prior to—or not more than 12hours to 18 hours after—initiation of antibiotics, and

quality performance measures for collection, transport, and processing of samples can be met. Sputum cultures in people with HIV have been shown to identify a bacterial etiology in up to 30-40% of good quality specimens[55,69] although yield is less in other studies.[14,29] Correlation of sputum culture with Gram stain can help in interpretation of sputum culture data. For intubated patients, an endotracheal aspirate sample should be obtained promptly after intubation, or bronchoscopy may be indicated.

Blood cultures are more likely to be positive in people with HIV than in those without HIV. Patients with HIV, particularly those with lower CD4 counts, are at increased risk of invasive infection with *S. pneumoniae*. Given concerns for drug-resistant *S. pneumoniae*[70,71], as well as *S. aureus* and/or other drug-resistant pathogens, blood cultures are recommended for patients with HIV who meet the criteria as noted above, and are optional for those who do not meet the criteria listed.

Diagnostic thoracentesis should be performed in all patients with pleural effusion if concern exists for accompanying empyema, and pleural fluid should be sent for microbiologic studies. Therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate-to-large-sized pleural effusion. Given the increased risk of invasive pneumococcal disease in patients with HIV, clinicians should be vigilant for evidence of extra-pulmonary complications of infection.

Preventing Exposure

No effective means exist to reduce exposure to *S. pneumoniae* and *Haemophilus influenzae*, which are common in the community. General precautions to maintain health, such as adhering to hand hygiene and cough etiquette and refraining from close contact with individuals who have respiratory infections, should be emphasized for patients with HIV as for other patient populations.

Preventing Disease

Pneumococcal Vaccine

Vaccination against *S. pneumoniae* is an important measure in preventing bacterial pneumonia. Some observational studies have reported benefits of pneumococcal polysaccharide vaccine (PPSV) use in people with HIV against IPD (e.g., bacteremia, meningitis)[49,72], and all-cause pneumonia;[73-75] however, results have been variable.[72,76-78] One randomized placebo-controlled trial of PPSV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia, and there was no evidence of reduced risk of IPD among vaccinated participants.[79] Follow-up of this cohort not only confirmed the increase in pneumonia in vaccinated participants, but also showed a decrease in all-cause mortality, although participants in this study were not treated with ART.[80] A recent study[81] evaluating the impact of the 13-valent pneumococcal conjugate vaccine (PCV13) vaccination on the rates of IPD in adults with HIV between 2008 and 2018 found that IPD rates remained high despite reductions with the introduction of PCV13. PCV20/non-PCV15 serotypes comprised 16.5% of cases of IPD, suggesting that the use of higher valent conjugate pneumococcal vaccines may reduce IPD.

In 2021, two PCVs, 15-valent (PCV15) and 20-valent (PCV20), were licensed by the FDA for use in U.S. adults.[82] PCV15 and PCV20 were licensed based on safety and immunogenicity data compared with the 13-valent PCV or 23-valent pneumococcal polysaccharide vaccine (PPSV23). Effectiveness data of these vaccine against pneumococcal disease in adults with HIV infection are currently not available. One phase 3 clinical trial of PCV15 followed by PPSV23 8 weeks later in people with HIV

demonstrated safety and immunogenicity of this approach.[83] No clinical data exist for the use of PCV20 in people with HIV. To date, one randomized, double-blind, placebo-controlled trial has assessed the efficacy of PCV against pneumococcal disease in adults with HIV. This was a trial on 7-valent PCV (PCV7) among adults with HIV in Malawi, which demonstrated 74% efficacy against vaccine-type IPD, with clear evidence of efficacy in those with CD4 counts <200 cells/mm^3.[84] However, study participants were those who had recovered from IPD, and received two doses of PCV7 four weeks apart. Therefore, findings may not be directly applicable to adults with HIV infection.

Patients with CD4 counts ≥200 cells/mm^3 should receive a dose of PPSV23 at least 8 weeks later **(AI)**.[72-75,85-89] While individuals with HIV with CD4 counts <200 cells/mm^3 can also be offered PPSV23 at least 8 weeks after receiving PCV15 **(CIII)** (such as if there are concerns with retention in care), PPSV23 should preferably be deferred until after an individual's CD4 count increases to >200 cells/mm^3 while on ART **(BIII).** Clinical evidence supporting use of PPSV23 in persons with CD4 counts <200 cells/mm^3 appears strongest in patients who also have HIV RNA <100,000 copies/mL;[75,89] evidence also suggests benefit for those who start ART before receiving PPSV vaccination.[72,90]

People with HIV who have received PCV13 but have not completed their recommended pneumococcal vaccine series with PPSV23, one dose of PCV20 may be used if PPSV23 is not available. If PCV20 is used, their pneumococcal vaccinations are complete **(CIII).**

Influenza Vaccine

Influenza vaccination is pertinent to prevention of CAP from influenza or influenza-associated bacterial pneumonia, which can occur as a complication of influenza. Influenza and pneumococcal vaccines can be administered during the same visit. Use of high-dose inactivated influenza vaccine is associated with decreased incidence of influenza and greater antibody response in adults without HIV age ≥65 years compared with standard-dose inactivated vaccine.[91,92] One trial found greater immunogenicity in people with HIV age ≥18 years who were given high-dose influenza vaccine compared with standard-dose inactivated vaccine.[93] See the "Influenza Vaccine" section in the Immunization section of the Adult and Adolescent Opportunistic Infections Guidelines for a detailed evidence summary.

All people with HIV infection during influenza season **(AI)** should be immunized against influenza with inactivated, standard dose or recombinant influenza vaccine per recommendation of the season **(AI).** High-dose inactivated influenza vaccine may be given to individuals age >65 years (AIII). For pregnant people with HIV, administer inactivated influenza or recombinant vaccine at any time during pregnancy **(AI).**

Additional Vaccines

The incidence of *H. influenzae* type b infection in adults with HIV is low. Therefore, *H. influenzae* type vaccine is not usually recommended for adult use **(BIII)**[90] unless a patient also has anatomic or functional asplenia.

Recommendations for COVID-19 vaccination are provided in the Immunization section of the Adult and Adolescent Opportunistic Infections Guidelines.

Prophylaxis and Risk Reduction

Several factors are associated with a decreased risk of bacterial pneumonia in HIV, including use of ART and trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis.[55] In many studies, daily administration of TMP-SMX for PCP prophylaxis reduced the frequency of bacterial respiratory infections.[9,94,95] This point should be considered when selecting an agent for PCP prophylaxis; however, indiscriminate use of TMP-SMX (when not indicated for PCP prophylaxis or other specific reasons) may promote development of TMP-SMX-resistant organisms. Thus, in the United States, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection **(AIII).** Similarly, clarithromycin or azithromycin should not be prescribed solely for preventing bacterial respiratory infection **(AIII).**

A decreased absolute neutrophil count (e.g., <500 cells/mm^3) is associated with an increased risk of bacterial infections, including pneumonia, although this risk has been demonstrated primarily in persons with malignant neoplasms. To reduce the risk of such bacterial infections, clinicians should take steps to reverse neutropenia, such as by stopping myelosuppressive drugs **(CIII).** Studies of granulocyte-colony stimulating factor (G-CSF) in people with HIV have failed to document benefit.[96,97]

Modifiable factors associated with an increased risk of bacterial pneumonia include smoking cigarettes, using injection drugs, and consuming alcohol.[9,74,98-100] Clinicians should encourage cessation of these behaviors, refer patients to appropriate services, and/or prescribe medications to support quitting. Data demonstrate that smoking cessation can decrease the risk of bacterial pneumonia.[15]

Treating Disease

General Approach to Treatment

The basic principles of antibiotic treatment of CAP are the same for patients with HIV as for those who do not have HIV.[67] As discussed in the Diagnosis section, if specimens are to be collected for diagnosis, they should preferably be collected before antibiotic therapy is initiated or within 12 hours to 18 hours of antibiotic initiation. However, antibiotic therapy should be administered promptly, without waiting for the results of diagnostic testing. Empiric therapy varies based on geographic region and common pathogens in these regions, and should take into account local resistance patterns, results of MRSA rapid swab testing if done, and individual patient risk factors, including severity of immunocompromise (recent CD4 cell count, HIV viral load) and use of ART.

In patients with HIV, providers must also consider the risk of opportunistic lung infections, such as PCP, that would alter empiric treatment. In settings where the prevalence of TB is high, initiation of empiric therapy for both bacterial pneumonia and TB may be appropriate for patients in whom both diagnoses are strong considerations and after diagnostic studies are undertaken. Because respiratory fluoroquinolones are also active against *M. tuberculosis,* they should be used with caution in patients with suspected TB who are not being treated with concurrent standard four-drug TB therapy. Thus, patients with TB who are treated with fluoroquinolones in the absence of standard four-drug TB therapy may have an initial, but misleading response, that could delay diagnosis of TB and initiation of appropriate multidrug TB therapy, increasing the risk of drug-resistant TB and TB transmission.

Assessing Severity of Disease and Treatment Location

Whether patients should be treated on an outpatient basis or admitted to the hospital depends on several factors. In addition to considerations regarding ability to take oral medications, adherence, and other confounding factors (housing, comorbid diseases, etc.), severity of illness is a key factor that helps to guide decisions regarding treatment location for CAP—outpatient versus inpatient, including intensive care unit (ICU). Notably, no prospective randomized clinical trials have assessed the performance of the Pneumonia Severity Index (PSI) for CAP or other severity scores (e.g., the ATS/IDSA severity criteria[67] or CURB-65 Score for Pneumonia Severity, to guide decisions regarding inpatient or outpatient treatment location for people with HIV. However, the PSI, CURB-65, the ATS/IDSA severity criteria, and other scoring systems appear to be valid for predicting mortality in patients with HIV with CAP, especially when used in combination with CD4 count.[59,101,102]

Whether the performance of severity indices is improved by including HIV-related variables is uncertain. One study suggested that the site of care decision be dictated by considering the PSI score and CD4 count together.[101] Mortality was increased in patients with higher PSI risk class; however, even in those without an increased mortality risk by PSI, a CD4 count <200 cells/mm^3 was associated with an increased risk of death.[101] This led to the suggestion to hospitalize CAP patients with CD4 counts <200 cells/mm^3 and to use the PSI to help guide decision-making in those with higher CD4 counts.[103]

However, other studies have found the PSI was predictive of outcomes independent of CD4 count.[104] Furthermore, CD4 count or HIV RNA level are not clearly associated with short-term outcomes of CAP.[105] Other HIV-specific scoring systems such as the Veterans Aging Cohort Study (VACS) Index, although originally designed to predict overall mortality, may also be useful in predicting ICU admission and mortality. In a study of older patients with and without HIV with CAP, a higher VACS Index was associated with greater 30-day mortality, readmission, and length of stay.[106] Another possible tool is the SWAT-Bp tool developed in Malawi.[107] This tool measures male [S]ex, muscle [W]asting, non-[A]mbulatory, [T]emperature (>38°C or <35°C), and [B]lood [p]ressure (systolic<100 and/or diastolic<60)). In a retrospective study of 216 patients (84% with HIV), demonstrated moderate discriminatory power, while the CURB-65 was less accurate.

Thus in general, validated clinical prediction scores for prognosis can be used in patients with HIV in conjunction with clinical judgement to guide treatment location for CAP. Low risk patients for whom there are no other concerns regarding adherence or complicating factors can be treated as outpatients. Patients with severe CAP, including those presenting with shock or respiratory failure, usually require a higher level of care, typically ICU admission. Additionally, severe CAP criteria can include PSI risk class of III or IV or CURB-65 scores ≥3. Patients with ≥3 of the ATS/IDSA minor severity criteria for CAP[67] often require ICU or higher level of care, as well.

Empiric Antibiotic Therapy by Treatment Setting and Severity of Diseases

There is a general paucity of clinical trials evaluating different antibiotic regimens for treating CAP in populations with HIV and a lack of evidence that treatment response to antibiotics is different in individuals with HIV than in those without HIV. Therefore, treatment recommendations for CAP in individuals with HIV are generally consistent with the ATS/IDSA guidelines for people without HIV.[67]

Outpatient CAP Treatment

Individuals with HIV who are being treated as outpatients should receive an oral beta-lactam plus a macrolide **(AI),** or a respiratory fluoroquinolone **(AI).** Preferred beta-lactams are high-dose amoxicillin or amoxicillin-clavulanate; alternatives are cefpodoxime or cefuroxime. Preferred macrolides are azithromycin or clarithromycin. Preferred respiratory fluoroquinolones are moxifloxacin or levofloxacin. A respiratory fluoroquinolone (moxifloxacin or levofloxacin) should be used as an alternative to a beta lactam in patients who are allergic to penicillin. If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative **(BIII)** in addition to a beta-lactam.

Empirical monotherapy with a macrolide for outpatient CAP is not routinely recommended in patients with HIV for two reasons **(BIII).** First, increasing rates of pneumococcal resistance have been reported with erythromycin-resistant rates up to 30%,[108] prompting concerns for possible treatment failure. In this regard, local drug resistance patterns, if available, can help inform treatment decisions. Additionally, patients who are already receiving a macrolide for MAC prophylaxis may have resistance due to chronic exposure, and should also not receive macrolide monotherapy for empiric treatment of bacterial pneumonia. However, macrolides can be used as part of a combination CAP regimen.

Non-Severe CAP Inpatient Treatment

Individuals with HIV who are being treated as inpatients should receive an intravenous (IV) beta-lactam plus a macrolide **(AI)** or a respiratory fluoroquinolone **(AI).** Monotherapy with a macrolide is not recommended in the inpatient setting. The role for dual therapy with a macrolide is somewhat controversial based on prior observational studies and two prospective clinical trials in patients without HIV with CAP that evaluated outcomes in those treated with beta-lactam monotherapy and those treated with dual-therapy including a macrolide.[109,110] In one study, beta-lactam monotherapy was not found to be non-inferior to beta-lactam/macrolide combination therapy. Notably, in the monotherapy arm, patients who had more severe CAP, as indicated by a PSI ≥IV, or who had atypical pathogens were less likely to reach clinical stability. There were also more 30-day readmissions among the patients on monotherapy.[109] While there was a trend towards improved outcomes in those on dual therapy, the difference between arms was not statistically significant. In a pragmatic, cluster-randomized, cross-over trial of non-ICU hospitalized patients with CAP, beta-lactam monotherapy was found to be non-inferior to beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy.[110] However in this study, the diagnosis of CAP did not require radiographic confirmation, illness was mild, and there were cross-overs between groups.

Only one study thus far has compared a cephalosporin (ceftriaxone) to dual therapy with a cephalosporin (ceftriaxone) plus macrolide in 225 people with HIV with CAP, finding no difference between in-hospital or 14-day mortality between the groups; most patients had lower severity of disease, with only 7% of the cohort having a CURB-65 score >2 and 17% with a PSI risk class >III.[111] Given the heterogeneity and limitations of recent studies and scarce data in patients with HIV, the recommendation for patients with HIV who are hospitalized with non-severe CAP remains that same as in people without HIV: to administer either beta-lactam/macrolide combination therapy, or a single drug regimen of a respiratory fluoroquinolone **(AI).**

Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Preferred macrolides are azithromycin and clarithromycin. Preferred respiratory fluoroquinolones are moxifloxacin or

levofloxacin. If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative **(BIII)** in addition to a beta-lactam. Clinical and Laboratory Standards Institute and U. S. Food and Drug Administration (FDA) changes in the penicillin breakpoints for treatment of non-meningitis pneumococcal disease imply IV penicillin is an acceptable option for treatment of pneumococcal disease in patients with HIV **(BIII).**[112] In patients who are allergic to penicillin, a respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) alone should be used **(AI).** As noted, fluoroquinolone monotherapy should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy.

Severe CAP Treatment

Patients with severe CAP should not receive empiric monotherapy, even with a fluoroquinolone, because of the range of potential pathogens and the desirability of prompt and microbiologically active therapy (AI). In one study, the use of dual therapy (usually with a beta-lactam plus a macrolide) was associated with reduced mortality in patients with bacteremic pneumococcal pneumonia, including those admitted to the ICU.[113] Patients with severe pneumonia should be treated with an IV beta-lactam plus either azithromycin **(AI)** or a respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) **(AI).** Both have a strong recommendation. Weak observational data, in the absence of prospective randomized controlled data, suggest that beta-lactam plus macrolide may be associated with decreased mortality.[77,114,115] Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. In patients who are allergic to penicillin, aztreonam plus a respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(BIII).**

The majority of CAP pathogens can be treated adequately with recommended empiric regimens. The increased incidence of *P. aeruginosa* and *S. aureus* (including community-acquired MRSA) as causes of CAP are exceptions. Both of these pathogens occur in specific epidemiologic patterns with distinct clinical presentations for which empiric antibiotic coverage may be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empiric treatment if results are negative. In the most recent ATS/IDSA CAP guidelines, empiric therapy for *P. aeruginosa* or MRSA is recommended in those with severe CAP, who have had these organisms previously isolated from sputum cultures, with de-escalation if these organisms are not isolated from current cultures.[67]

The addition of corticosteroids for treating CAP has not been studied in people with HIV. Data from studies in people without HIV with CAP suggest that corticosteroids may decrease a composite outcome of mortality, time to clinical stability, and length of hospital stay.[116] Importantly, effects of corticosteroids appear variable according to etiology and severity of pneumonia, however, as corticosteroids may increase mortality in influenza pneumonia,[117] but decrease mortality in patients with COVID-19 who require higher levels of respiratory support.[118] The optimal regimen including dose, duration, and formulation of corticosteroid, and the patient population with bacterial non-viral related CAP most likely to benefit from the additional use of corticosteroids remain uncertain. Selecting HIV-uninfected patients with severe CAP and increased inflammation as defined by C-reactive protein levels >150 mg/mL is one strategy for treatment of CAP that has been shown to be beneficial.[119]

ATS/IDSA guidelines recommend not using corticosteroids routinely in non-severe **(AI)** or severe CAP **(BII)** but endorse use in CAP with refractory shock[67] Similarly, the use of corticosteroids in HIV-infected patients with severe CAP is not routinely recommended **(BII)** given the lack of data

specifically in HIV-infected population. If providers administer corticosteroids to HIV-infected patients with severe CAP, they must ensure that no other contraindications to steroids exist; in patients who have no contraindications and have persistent shock despite fluid resuscitation, Surviving Sepsis Guidelines[120] provide a weak recommendation for administering hydrocortisone 200 mg IV daily for 5 to 7 days or tapering once vasopressors are no longer needed.

Empiric **Pseudomonas aeruginosa** *Treatment*

If risk factors for *Pseudomonas* infection are present, an antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin (750-mg dose) should be used **(AI).** Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. Alternative therapeutic agents that are recommended are an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin **(BII)** or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone **(BII).** In patients who are allergic to penicillin, aztreonam is recommended to be used in place of the beta-lactam **(BII).**

Empiric **Staphylococcus aureus** *Treatment*

A nasal swab for MRSA can help inform decision-making whether initial empiric coverage should include MRSA. In studies of patients without HIV, negative test results have a high negative predictive value for pneumonia due to MRSA. If the nasal swab is negative for MRSA and the pneumonia is not severe and no other risk factors or features suggestive of MRSA pneumonia are present, empiric coverage for MRSA may be withheld **(BII).**[68]

However, in patients who have risk factors for *S. aureus* infection, vancomycin or linezolid should be added to the antibiotic regimen **(AII).** Empiric coverage for MRSA should also be added if a rapid nasal swab is positive for MRSA, although the positive predictive value for pneumonia is only moderate, and therapy should be de-escalated if cultures are negative **(BIII).** Although not routinely recommended, the addition of clindamycin to vancomycin (but not to linezolid) or the use of linezolid alone, is recommended by many experts if severe necrotizing pneumonia is present to minimize bacterial toxin production **(CII).**

Telavancin is an alternative agent that can be used for *S. aureus* pneumonia **(BIII);** it is currently FDA-approved for treatment of hospital-acquired and ventilator-associated (rather than community-acquired) pneumonia based on studies in people without HIV infection.[121] While ceftaroline has activity against MRSA, and data suggest it can be effective for MRSA pneumonia, it has been FDA approved for treatment of bacterial CAP based on two studies that did not include any MRSA isolates.[122] Neither telavancin or ceftaroline have been specifically studied in patients with HIV with bacterial pneumonia. Daptomycin should not be used to treat pneumonia as it is not active in the lung **(AI).**

Pathogen-Directed Therapy

When the etiology of the pneumonia has been identified based on reliable microbiological methods, antimicrobial therapy should be modified and directed at the identified pathogen **(BIII).**

Switch From Intravenous to Oral Therapy

A switch to oral therapy should be considered in patients with CAP on IV antibiotic therapy who have improved clinically, can swallow and tolerate oral medications, and have intact gastrointestinal function.[67] A longer duration of IV and overall antibiotic therapy is often necessary in patients who have severe CAP or who have bacteremia, particularly if due to *S. pneumoniae* or *S. aureus* and complicated infection is present.

Special Considerations Regarding When to Start Antiretroviral Therapy

In patients with bacterial pneumonia who are not already on ART, ART should be initiated promptly (i.e., within 2 weeks of initiating therapy for the pneumonia) unless comorbidities make ART unwise **(AI)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

The clinical response to appropriate antimicrobial therapy for CAP is similar in patients with and without HIV.[43,58] A clinical response (i.e., reduction in fever and improvement in respiratory symptoms, physical findings, and laboratory studies) typically is observed within 48 to 72 hours after initiation of appropriate antimicrobial therapy. A review of patients with CAP found that advanced HIV infection and CD4 count <100 cells/mm^3 were predictors for longer time to clinical stability (i.e., >7 days) and that patients who received ART tended to become clinically stable sooner and had better outcomes.[103,106] The presence of bacteremia is a significant factor that impacts outcomes. Among those with pneumococcal pneumonia, longer time to clinical stability is more often seen in the setting of bacteremia. As in patients without HIV, radiographic improvement usually lags behind clinical improvement.

Immune reconstitution inflammatory syndrome (IRIS) has been rarely described in association with bacterial CAP and initiation of treatment with ART in patients with HIV. This could be secondary to a number of reasons: 1) patients with recurrent pneumonia have not been included in the study population; 2) IRIS among participants with bacterial pneumonia has not been specified or 3) this complication has truly not been observed.[2,123] Only case reports describe IRIS with pneumonia due to *Rhodococcus equii*. More commonly IRIS occurs with pneumonia due to *Pneumocystis* and mycobacterial infections.

Managing Treatment Failure

Patients who do not respond to appropriate antimicrobial therapy should undergo further evaluation to search for complications secondary to pneumonia (empyema, abscess formation, metastatic infection), other infectious process, the presence of a drug-resistant pathogen, and/or noninfectious causes of pulmonary dysfunction (pulmonary embolus, COPD).

Preventing Recurrence

Patients with HIV should receive pneumococcal **(AI)** and influenza vaccines **(AI)** as recommended. Antibiotic chemoprophylaxis generally is not recommended specifically to prevent recurrences of bacterial respiratory infections because of the potential for development of drug-resistant microorganisms and drug toxicity **(AI).** Smoking cessation reduces the risk of bacterial pneumonia (by approximately 27%),[124] and patients who smoke tobacco should be encouraged to quit and

provided with the appropriate tools and referrals whenever possible **(AI).** Likewise, patients with substance use disorders (alcohol, injection or non-injection drugs) should be referred for appropriate counseling and services **(AI).** However, likely the most important intervention for prevention of bacterial pneumonia (first episode or recurrence) is initiation and adherence to ART, which is beneficial even among those with high CD4 count at time of ART initiation.[4] Thus prompt initiation or re-initiation of ART is recommended for all patients with HIV with bacterial pneumonia **(AI).**

Special Considerations During Pregnancy

The diagnosis of bacterial respiratory tract infections in pregnant women is the same as in those who are not pregnant, with appropriate shielding of the abdomen during radiographic procedures. Bacterial respiratory tract infections should be managed in pregnant women as in women who are not pregnant, with certain exceptions. Among macrolides, clarithromycin is not recommended because of an increased risk of birth defects seen in some animal studies. Two studies, each involving at least 100 women with first-trimester exposure to clarithromycin, did not document a clear increase in or specific pattern of birth defects, although an increased risk of spontaneous abortion was noted in one study.[125,126] Azithromycin did not produce birth defects in animal studies, but experience with human use in the first trimester is limited. Azithromycin is recommended when a macrolide is indicated in pregnancy **(BIII).** Arthropathy has been noted in immature animals with *in utero* exposure to quinolones. Studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[127,128] When indicated, quinolones can be used in pregnancy for serious respiratory infections only when a safer alternative is not available **(CIII).**[129]

Doxycycline is not recommended for use during pregnancy because of increased hepatotoxicity and staining of fetal teeth and bones. Beta-lactam antibiotics have not been associated with teratogenicity or increased toxicity in pregnancy. Clindamycin use in pregnancy has not been associated with an increased risk of birth defects or adverse outcomes.[130] Aminoglycosides can be used as needed. A theoretical risk of fetal renal or eighth nerve damage exists with aminoglycoside exposure during pregnancy, but this finding has not been documented in humans, except with streptomycin (10% risk) and kanamycin (2% risk). Animal reproductive toxicity studies in rats and rabbits were negative for vancomycin, but data on first trimester exposure in humans are limited.[131] A study of neonates after in utero exposure did not find evidence of renal or ototoxicity.[132] Reproductive toxicity studies of televancin in animals have shown increased rates of limb malformations in rats, rabbits, and mini pigs at doses similar to human exposure; no human data are available.[131] Use of telavancin should be avoided in the first trimester if alternate agents with more experience in use in pregnancy are available. Cases of exposure to telavancin in pregnancy should be reported to the Televancin Pregnancy Registry at 1-855-633-8479. Experience with linezolid in human pregnancy has been limited, but it was not teratogenic in mice, rats, and rabbits.

Pneumonia during pregnancy is associated with increased rates of preterm labor and delivery. Pregnant women with pneumonia after 20 weeks' gestation should be monitored for evidence of contractions **(BII).** Pneumococcal vaccine can be administered during pregnancy **(AIII).** A study comparing administration of PCV10, PPSV23, or control (1:1:1) among 347 women during weeks 13–34 of pregnancy found that PCV10 and PPSV23 were equally safe and immunogenic in pregnant women with HIV and conferred similar levels of seroprotection to their infants.[133] No adverse consequences have been reported among newborns whose mothers were vaccinated during pregnancy. Women who did not receive vaccines during pregnancy were vaccinated post-partum; these data demonstrated higher antibody responses compared to women vaccinated ante-partum, suggesting that postpartum booster doses may be beneficial and require further study.[134]

Inactivated influenza vaccine is recommended for all pregnant women during influenza season **(AI).** Live attenuated influenza vaccine should not be used in people with HIV **(AIII).** Because administration of vaccines can be associated with a transient rise in plasma HIV RNA levels, vaccination of pregnant women is recommended after ART has been initiated to minimize increases in plasma HIV RNA levels that might increase the risk of perinatal transmission of HIV.

Recommendations for Preventing and Treating Community-Acquired Pneumonia

Preventing *Streptococcus pneumoniae* Infections

Indications for Pneumococcal Vaccination

- All people with HIV regardless of CD4 count **(AI)**

Vaccination Recommendations

- For all people with HIV without history of pneumococcal vaccination or unknown vaccine history:
    - Administer either 15-valent pneumococcal conjugate vaccine (PCV15) or 20-valent pneumococcal conjugate vaccine (PCV20) **(AII).** If PCV20 is used, their pneumococcal vaccination is complete.
    - If PCV15 is used, a dose of PPSV23 should be administered at least 8 weeks later **(AII).*** No additional pneumococcal vaccine doses are recommended.

- For people with HIV who previously started or completed a pneumococcal vaccination series, there is no need to restart the series.**
    - People with HIV who received PCV13 and were 65 or older when they received a dose of PPSV23 do not require further doses of PPSV23; for those who received PPSV23 younger than age 65, additional doses of PPSV23 are recommended as indicated below **(BIII).**
        - People with HIV who have received PCV13 and PPSV23 at age <65 should receive a second dose of PPSV23 at least 5 years after the first dose. If they are age 65 or older at the time of their second dose, they do not require additional doses of PPSV23.
        - If they were <65 at the time of the second dose, they should receive a third and final dose at or after age 65, at least 5 years after the second PPSV23 dose.
    - People with HIV who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23 at any age **(BIII).**

Footnotes

* Patients with CD4 counts $\geq$200 cells/mm^3 should receive a dose of PPSV23 at least 8 weeks later **(AI).** While individuals with HIV with CD4 counts <200 cells/mm^3 can also be offered PPSV23 at least 8 weeks after receiving PCV15 **(CIII)** (such as if there are concerns with retention in care), PPSV23 should preferably be deferred until after an individual's CD4 count increases to >200 cells/mm^3 while on ART **(BIII).** Clinical evidence supporting use of PPSV23 in persons with CD4 counts <200 cells/mm^3 appears strongest in patients who also have HIV RNA <100,000 copies/mL; evidence also suggests benefit for those who start ART before receiving PPSV vaccination.

** People with HIV who have received PCV13 but have not completed their recommended pneumococcal vaccine series with PPSV23, one dose of PCV20 may be used if PPSV23 is not available. If PCV20 is used, their pneumococcal vaccinations are complete **(CIII).**

Preventing Influenza and Bacterial Pneumonia as a Complication of Influenza

Indication for Influenza Vaccination

- All people with HIV infection during influenza season **(AI)**

Vaccination

- Adults age ≥65 years are recommended to receive high-dose IIV (Fluzone® High-Dose) or adjuvanted IIV (FLUAD®) over standard-dose unadjuvanted vaccine **(AII).**

- People age ≥18 years also may use RIV (Flublok® Quadrivalent).

Recommendations for Preventing and Treating Community-Acquired Pneumonia

- For people with egg allergy, use IIV or RIV appropriate for age (if the allergic reaction is more severe than hives, give the vaccine in a medical setting appropriate to manage severe allergic reaction).

- For pregnant people with HIV, administer inactivated influenza or recombinant vaccine at any time during pregnancy **(AI)**.

- Influenza vaccines are quadrivalent, with formulations that change from season to season.

Note: Live attenuated influenza vaccine is contraindicated in people with HIV **(AIII)**.

Treating Community-Acquired Bacterial Pneumonia

Note: Empiric antimicrobial therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed below are suggested empiric therapy. The regimen should be modified as needed once microbiologic and drug susceptibility results are available. Providers must also consider the risk of opportunistic lung infections such as PCP or TB, which may alter the empiric therapy as needed.

Empiric Outpatient Therapy (Oral)

Preferred Therapy

- An oral beta-lactam + a macrolide (azithromycin or clarithromycin) **(AI)**
  - *Preferred beta-lactams*: high-dose amoxicillin or amoxicillin/clavulanate
  - *Alternative beta-lactams:* cefpodoxime or cefuroxime

or

- A respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] **(AI)**, especially for patients with penicillin allergies.

Alternative Therapy

- A beta-lactam + doxycycline **(BIII)**

Empiric Therapy for Hospitalized Patients with Non-Severe CAP

Preferred Therapy

- An IV beta-lactam + a macrolide (azithromycin or clarithromycin) **(AI)**
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam

or

- A respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] **(AI)**, especially for patients with penicillin allergies.

Alternative Therapy

- An IV beta-lactam + doxycycline **(BIII)**
- IV penicillin may be used for confirmed pneumococcal pneumonia **(BIII)**

Empiric Therapy for Patients with Severe CAP

Preferred Therapy

- An IV beta-lactam + azithromycin **(AI)**, *or*
- An IV beta-lactam + a respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] **(AI)**
  - *Preferred beta-lactams*: ceftriaxone, cefotaxime, or ampicillin-sulbactam

Alternative Therapy

For Penicillin-Allergic Patients

- Aztreonam (IV) + a respiratory fluoroquinolone (moxifloxacin or levofloxacin)[a] **(BIII)**

Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia

Recommendations for Preventing and Treating Community-Acquired Pneumonia

Preferred Therapy

- An IV antipneumococcal, antipseudomonal beta-lactam + (ciprofloxacin IV or levofloxacin IV 750 mg/day) **(AI)**
  - *Preferred beta-lactams*: piperacillin-tazobactam, cefepime, imipenem, or meropenem

Alternative Therapy

- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + IV azithromycin **(BII)**, *or*

- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + an antipneumococcal fluoroquinolone (moxifloxacin or levofloxacin) **(BII)**

For Penicillin-Allergic Patients

- Replace the beta-lactam with aztreonam **(BII)**.

Empiric Therapy for Patients at Risk of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Pneumonia

Preferred Therapy

- A nasal swab for MRSA can help inform decision of initial coverage for MRSA (see text for discussion)

- Vancomycin IV or linezolid (IV or PO) should be added to the baseline regimen **(AII)**.

- Although not routinely recommended, the addition of clindamycin to vancomycin (but not to linezolid) may be considered for severe necrotizing pneumonia to minimize bacterial toxin production **(CII)**.

Duration of Therapy

- For most patients: 5–7 days. The patient should be afebrile for 48–72 hours, and should be clinically stable before discontinuation of therapy.

- Longer duration of antibiotics is often required if severe CAP or bacteremia is present, and particularly if due to *S. pneumoniae* or complicated *S. aureus* infection.

Switch from IV to PO Therapy

- A switch should be considered for patients who have improved clinically, can swallow and tolerate oral medications, and have intact gastrointestinal function **(BIII)**.

Other Considerations

- Empiric therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance (up to 30%) **(BIII)**, and patients receiving a macrolide for MAC prophylaxis may have resistance due to chronic exposure **(BIII)**.

- Fluoroquinolones should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy **(BIII)**.

- Once the pathogen has been identified by reliable microbiologic methods, antibiotic therapy should be modified to target the pathogen **(BIII)**.

- If drug-resistant pathogens have not been identified by reliable microbiologic methods, antibiotic therapy can be de-escalated to cover routine causes of CAP **(BIII)**.

- Antibiotics chemoprophylaxis is generally not recommended because of the potential for development of drug resistance microorganisms and drug toxicities (**AI**).

[a] Respiratory fluoroquinolones such as levofloxacin or moxifloxacin are also active against *Mycobacterium tuberculosis.* In patients with undiagnosed TB, fluoroquinolones may alter response to therapy, delay TB diagnosis, and increase the risk of drug resistance. These drugs should be used with caution in patients in whom TB is suspected but who are not receiving a standard 4-drug TB regimen.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; IM = intramuscularly; IV = intravenously; MAC = *Mycobacterium avium* complex; MRSA = methicillin-resistant *Staphylococcus aureus;* PCV13 = 13-Valent Pneumococcal Conjugate Vaccine; PO = orally; PPSV23 – 23-Valent Pneumococcal Polysaccharide Vaccine; TB = tuberculosis

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Cryptococcosis

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Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the cause. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the U.S. Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of people with advanced HIV in some high-resourced countries had disseminated cryptococcosis.[1] In a surveillance study in the late 1990s, people with HIV who developed cryptococcosis were severely immunosuppressed and had barriers to accessing routine HIV medical care.[2] Estimates indicate that every year, approximately 280,000 cases of cryptococcal infection in people with AIDS occur worldwide, and the disease accounts for 15% of AIDS-related deaths.[3] Overall, 90% of cryptococcal cases in people with HIV are observed in those who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3. The incidence of the disease has declined substantially among people treated effectively with ART.[4]

Clinical Manifestations

In people with HIV, cryptococcosis commonly presents as subacute meningitis or meningoencephalitis with fever, malaise, and headache slowly developing over many weeks, with a median duration of 2 weeks.[1] Classic meningeal symptoms and signs—such as neck stiffness and photophobia—occur in only one-quarter to one-third of people. Some individuals experience encephalopathic symptoms—such as lethargy, altered mentation, personality changes, and memory loss—that are usually a result of increased intracranial pressure (ICP).[5] Among people presenting with cryptococcal meningitis shortly after initiating ART, the symptom onset can be more acute, likely related to an unmasking immune reconstitution inflammatory syndrome (IRIS).[6]

Despite manifesting principally as a central nervous system (CNS) disease, cryptococcosis may involve any bodily organ. In fact, despite widespread disseminated disease, people with HIV may manifest few symptoms. Skin lesions may show different manifestations, including umbilicated skin lesions that mimic those seen with molluscum contagiosum. Isolated pulmonary infection is also possible; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although nodular infiltrates have been reported. Pulmonary cryptococcosis may present as acute respiratory distress syndrome and even mimic *Pneumocystis* pneumonia.

Diagnosis

In people with HIV, cryptococcosis is usually disseminated at the time of diagnosis and most commonly presents as subacute meningoencephalitis. Analysis of cerebrospinal fluid (CSF) in initial cases generally demonstrates mildly elevated protein levels, low-to-normal glucose concentrations, and a variable presence of pleocytosis consisting mostly of lymphocytes. Some people with advanced HIV may have very few CSF inflammatory cells. A Gram stain or an India ink preparation, if available, may reveal numerous yeast forms. In patients with HIV and cryptococcal meningitis, the

opening pressure for the CSF may be elevated, with pressures ≥25 cm CSF in 60% to 80% of patients.[7,8]

Cryptococcal disease can be diagnosed by culture, CSF microscopy, cryptococcal antigen (CrAg) detection, or CSF polymerase chain reaction (PCR). In HIV-related cryptococcal meningitis, most blood cultures and CSF cultures will be positive (47% to 70% and 90% to 94%, respectively).[5] Visible *Cryptococcus* colonies on a fungal Sabouraud dextrose agar plate, or even a standard aerobic bacterial culture, generally can be detected within 7 days. *Cryptococcus* may be identified occasionally on a routine Gram stain preparation of CSF as poorly staining Gram-positive yeasts. India ink staining of CSF demonstrates encapsulated yeasts in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. India ink is relatively insensitive early in disease when <1,000 *Cryptococcus* colony-forming units (CFU)/mL are present.[9] In tissue or fluids, yeasts will stain with Grocott methenamine silver stain, and the capsule will stain with mucicarmine or alcian blue stains. Positive cultures are required to prove yeast viability because strains can be stain positive with nonviable yeasts.

Cryptococcus can infect any part of the body, but brain and lungs are frequently target organs. Cultures and/or histopathology are essential for precise diagnosis. However, in many patients with advanced HIV, the presentation is more commonly a meningeal syndrome rather than a pulmonary syndrome.

CSF CrAg is usually positive in people with cryptococcal meningoencephalitis; however, early meningitis can present with negative CSF studies and a positive CrAg in blood only.[10] Thus, serum CrAg testing always should be performed in an immunocompromised individual with an unknown CNS disorder.[10] Serum CrAg is positive in both meningeal and non-meningeal cryptococcal infections and may be present weeks to months before symptom onset.[11] All positive CrAg tests in patients with HIV require consideration for therapy.

Three methods exist for antigen detection: latex agglutination, enzyme immunoassay (EIA), and lateral flow assay (LFA). The IMMY CrAg LFA (IMMY, Norman, Oklahoma) is the only LFA test for CrAg approved by the U.S. Food and Drug Administration (FDA). It is a useful initial screening tool for diagnosing cryptococcosis in people with HIV when applied to serum or plasma,[9,12] and it also can be used with whole blood or CSF. CrAg testing of serum or plasma may be particularly useful when a lumbar puncture is delayed or refused. In a person with HIV, when serum CrAg LFA titers are ≥1:160, disseminated disease becomes increasingly more likely, and when CrAg LFA titers are ≥1:640, or when there is high clinical suspicion, disseminated and/or CNS involvement should be assumed, regardless of CSF antigen titer results.[13,14] Antigen titers by the LFA are approximately fourfold higher than those with latex agglutination or EIA testing; thus, a titer of 1:640 by LFA is approximately equal to a titer of 1:160 by EIA or latex agglutination. A prozone effect needs to be checked when CrAg with latex agglutination and LFA testing is negative despite observing yeasts in tissues or fluids.

In 2016, the BioFire FilmArray Meningitis/Encephalitis Panel PCR assay (BioFire Diagnostics, Salt Lake City, Utah) was approved by the FDA. This multiplex PCR tests for 14 targets, including *C. neoformans* and *C. gattii,* and performs well in infections with a moderate-to-high fungal burden.[15-17] False negative results have been noted to occur when there is a low burden of yeasts; in one study, when there were <100 CFU/mL, the sensitivity of the PCR test fell to 50%.[15] In one well-described case, a woman who had two negative results with this PCR assay later had a positive result on a CrAg test done by IMMY LFA.[18] Thus, a negative CSF PCR does not completely exclude

cryptococcal meningitis, and CrAg testing of CSF and blood should always be performed simultaneously. The PCR assay appears to have diagnostic utility when a second episode of cryptococcal meningitis is suspected; the test has been noted to differentiate a relapse (PCR positive) from IRIS (PCR negative).[15]

Preventing Exposure

Cryptococcus is ubiquitous in the environment, and people with HIV cannot completely avoid exposure to *C. neoformans* or *C. gattii.* Limited epidemiological evidence suggests that exposure to dried bird droppings, including those from chickens and pet birds, may increase the risk of infection and should be avoided. It is likely that many patients are infected with mixed strains of *Cryptococcus* over a lifetime, and clinical implications remain uncertain.[19,20]

Preventing Disease

The incidence of cryptococcal disease is low among people with HIV in the United States. However, one report indicates that among study participants with HIV in the United States with peripheral blood CD4 counts ≤100 cells/mm^3, the prevalence of cryptococcal antigenemia—a harbinger of disease—was 2.9%, and for those with CD4 counts ≤50 cells/mm^3, the prevalence was 4.3%.[21] Routine surveillance testing for serum CrAg in people with newly diagnosed HIV who have no overt clinical signs of meningitis is recommended for patients whose CD4 counts are ≤200 cells/mm^3 and particularly in those with CD4 counts ≤50 cells/mm^3 **(AII).**[22] All positive tests generally should prompt CSF evaluation for CNS infection, particularly when the serum LFA titer is ≥1:160 **(AII).**[23] See section on Treatment of Asymptomatic Antigenemia.

Prospective controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in people with HIV who have CD4 counts <100 cells/mm.[24,25] However, in the United States, primary prophylaxis in the absence of a positive serum CrAg test is not recommended because of the relative infrequency of cryptococcal disease, lack of clear survival benefit associated with prophylaxis,[26] possibility of drug–drug interactions, potential development of antifungal drug resistance, and cost **(BII).**

Treating Disease

Recommendations for Treating Cryptococcosis
Treating CNS and/or Disseminated Disease
Treatment consists of three phases: induction, consolidation, and maintenance therapy. **Induction Therapy (Duration: 2 Weeks, Followed by Consolidation Therapy)** • Irrespective of which regimen is used, patients must be followed carefully in the hospital for at least 7 days and ideally 14 days **(AII)**. LP should be performed at Day 7 and Day 14 to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily LP should be performed until the pressure is decreased into the normal range and symptoms have abated **(AII)**. *Preferred Regimens* • In the United States and other settings where daily monitoring of electrolytes and kidney function and administration of electrolytes and IV fluid is possible: ○ Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks **(AII)**

- In resource-limited health care systems, as recommended by the World Health Organization:
  - Liposomal amphotericin B 10 mg/kg IV as a single dose on Day 1, followed by flucytosine 25 mg/kg PO four times a day plus fluconazole 1,200 mg PO daily for 2 weeks **(AI)**

Alternative Regimens

- Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks **(BII)**, *or*

- Amphotericin B deoxycholate 1 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 1 week, followed by fluconazole 1,200 mg PO daily for an additional week **(BI)**

Note: The flucytosine dose should be adjusted in renal impairment and ideally use TDM (see Table 6).

Additional Studied Regimens (Duration of Therapy: 2 Weeks)

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day **(BI)**

- Liposomal amphotericin B 3–4 mg/kg IV once daily plus fluconazole 800–1,200 mg PO once daily **(BIII)**

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus fluconazole 800–1,200 mg PO once daily **(BI)**

- Fluconazole 1,200 mg PO or IV once daily plus flucytosine 25 mg/kg PO four times a day **(BII)**

If the patient has not improved clinically or remains clinically unstable, continue or start (liposomal amphotericin B or amphotericin B deoxycholate) plus flucytosine induction therapy until the CSF culture is confirmed to be negative **(BIII)**.

Additional Considerations

- CSF opening pressure should always be measured when an LP is performed. Repeated therapeutic LPs are essential to manage symptomatic increased ICP and have a survival benefit **(AII)**.

- Corticosteroids should not be used routinely during induction therapy unless used for management of IRIS **(AI)**.

- Corticosteroids, acetazolamide, and mannitol are ineffective in reducing ICP and **are not recommended (AIII)**.

Consolidation Therapy (Duration of Therapy: ≥8 Weeks, Followed by Maintenance Therapy)

Perform LP after 1 week and/or 2 weeks of induction therapy to document the culture is negative **(AII)**. After 2 weeks of induction therapy, people who are clinically stable may be switched to consolidation therapy while awaiting culture results. Duration of consolidation therapy should be for at least 8 weeks after receiving CSF culture at 2 weeks is negative **(AII)**.

Preferred Regimen

- Fluconazole 800 mg PO daily **(AI)**

- For clinically stable patients, continue fluconazole 800 mg until CSF cultures are known to be sterile and ART has been initiated; dose then can be reduced to 400 mg PO daily **(AII)**.

- If CSF remains positive in a clinically stable patient after 2 weeks of induction therapy, use one of the following two options for an additional 2 weeks before reducing the dose to fluconazole 800 mg PO daily:
  - Fluconazole 1,200 mg PO daily plus flucytosine 25 mg/kg PO four times a day for an additional 2 weeks **(BIII)**, or
  - Fluconazole 1,200 mg PO daily for an additional 2 weeks **(BIII)**

Alternative Regimen

- Itraconazole 200 mg PO twice a day, if fluconazole is not available or not tolerated **(CI)**

Maintenance Therapy

Preferred Regimen

- Fluconazole 200 mg PO once daily for ≥1 year from initiation of antifungal therapy (**AI**)

Alternative Regimen

- Itraconazole 200 mg PO twice a day, if fluconazole is not available or not tolerated (**CI**)

- If susceptibility studies have been performed and the fluconazole MIC is ≥16 µg/mL, the fluconazole dose may be increased to 400 mg daily (**BIII**).

Criteria for Stopping Maintenance Therapy (BII)

- At least 1 year from initiation of antifungal therapy, *and*

- Patient remains asymptomatic from cryptococcal infection, *and*

- CD4 count ≥100 cells/mm^3 and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy

- If CD4 count declines to <100 cells/mm^3 (**AIII**)

Treating Non-CNS Extrapulmonary Disease, Diffuse Pulmonary Disease, or Non-CNS Symptoms With Normal CSF and Serum CrAg Titer ≥1:640 by LFA (or ≥1:160 by EIA or Latex Agglutination)

Administer the same treatment as for patients with cryptococcal meningitis to people with the following conditions:

- Non-CNS extrapulmonary disease (**BIII**)

- Diffuse pulmonary disease (**BIII**)

- Non-CNS symptoms, normal CSF, and serum CrAg titer ≥1:640 by LFA (or ≥1:160 by EIA or latex agglutination) (**BII**)

Note: All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease.

Treating Non-CNS Focal Pulmonary Infiltrates (With Mild Symptoms) and Negative Serum CrAg

- Fluconazole 400 mg daily for 6 to 12 months (duration guided by symptom resolution) (**BIII**)

Treating Isolated Asymptomatic Cryptococcal Antigenemia (Serum CrAg Titer of LFA <1:640 [or <1:160 by EIA or Latex Agglutination])

- Fluconazole 800–1,200 mg PO daily for 2 weeks, followed by fluconazole 400–800 mg PO daily for 10 weeks, then fluconazole 200 mg PO daily for a total of 6 months plus effective ART (**BIII**)

Note: Those with lower risk and serum CrAg titer <1:80 by LFA (<1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture (**AI**). All others should undergo CSF sampling to rule out CNS disease.

Treatment in Pregnancy

Preferred Therapy During First Trimester

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (**AIII**), *or*

- Lipid formulation amphotericin B 3–4 mg/kg IV daily (**AIII**)

- Addition of flucytosine should be considered only when the benefits outweigh the risks, with delay until after the first trimester when feasible (**AIII**).

Notes: Optimal dosing of liposomal amphotericin B in pregnancy is unknown. Use of ideal body weight rather than total body weight may minimize risk of adverse effects to the fetus while maintaining efficacy **(BII)**. In general, azole antifungal agents should be avoided in the first trimester of pregnancy because of potential teratogenic effect, unless benefit is felt to outweigh risk **(BIII)**.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrAg = cryptococcal antigen; CSF = cerebrospinal fluid; EIA **=** enzyme immunoassay; ICP = intracranial pressure; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LFA = lateral flow assay; LP = lumbar puncture; MIC = minimum inhibitory concentration; PO = orally; TDM = therapeutic drug monitoring

Treatment of Central Nervous System and/or Disseminated Disease

Treatment of CNS and disseminated disease consists of three phases: induction, consolidation, and maintenance.

Induction Therapy

For induction treatment of cryptococcal meningitis and other forms of extrapulmonary cryptococcosis, an amphotericin B formulation given intravenously (IV), in combination with oral flucytosine, is recommended for 2 weeks in a resource-available health care system **(AII),** and in resource-limited health care systems, a single dose of liposomal amphotericin B (10 mg/kg) is recommended, followed by 2 weeks of flucytosine and fluconazole **(AI).** Historically, amphotericin B deoxycholate at a dose of 0.7 to 1.0 mg/kg daily had been the preferred formulation of the drug.[27] In resource-available health care systems, however, lipid formulations of amphotericin B have become the standard polyene formulations because they are effective for cryptococcosis and have lower toxicity. A study that compared amphotericin B deoxycholate (0.7 mg/kg daily) and liposomal amphotericin B (AmBisome) at two doses (3 mg/kg daily and 6 mg/kg daily) showed similar outcomes for all three regimens; however, lower nephrotoxicity was observed among those receiving the 3 mg/kg daily liposomal amphotericin B regimen.[28] The noncomparative CLEAR study demonstrated a 58% response rate in people with HIV and cryptococcosis who were treated with amphotericin B lipid complex (Abelcet) at a mean dose of 4.4 mg/kg daily.[29]

Several large clinical trials that used shorter courses of amphotericin B have been reported from Africa.[30,31] A multicenter clinical trial that evaluated two different induction regimens in 721 African adults with HIV found that an initial regimen of 1 week of amphotericin B deoxycholate at 1 mg/kg/day and flucytosine 25 mg/kg four times daily, followed by 1 week of oral fluconazole 1,200 mg/day was non-inferior (95% confidence interval [CI], -12.5 to 5.35 at 10 weeks) to the standard regimen of 2 weeks of amphotericin B deoxycholate 1 mg/kg/day and flucytosine 25 mg/kg four times daily when outcomes at 10 weeks were studied.[30] At 1 year, follow-up of 236 participants from this treatment trial continued to show noninferiority of the 1-week amphotericin B deoxycholate regimen compared with the 2-week regimen.[32]

A phase 3 open-label, randomized, controlled noninferiority trial of single-dose liposomal amphotericin B was conducted at five sites in Africa in 814 patients.[33] Results of this study showed that outcomes of people receiving a single dose of liposomal amphotericin B, 10 mg/kg, combined with 14 days of oral flucytosine, 25 mg/kg four times daily, and oral fluconazole, 1,200 mg/day, were not inferior to a control group that received therapy with amphotericin B deoxycholate, 1 mg/kg/day, and flucytosine, 25 mg/kg four times daily for 7 days, followed by oral fluconazole, 1,200 mg/day for another 7 days.[33] At 10 weeks, deaths were reported in 101 participants (24.8%; 95% CI, 20.7–29.3) in the liposomal amphotericin B group and 117 participants (28.7%; 95% CI, 24.4–33.4) in the control group (difference, −3.9 percentage points); the upper boundary of the one-sided

95% CI was 1.2 percentage points (within the noninferiority margin; P <0.001 for noninferiority). Grade 3 or 4 toxicity was reduced in the single-dose liposomal amphotericin B group compared with the amphotericin B deoxycholate group (50% vs. 62.3%, P <0.001).[33] It is important to note that patients in both groups were monitored closely in a hospital for a minimum of 7 days. Lumbar punctures were performed on Day 7 and Day 14 and daily if ICP was >25 cm of CSF or if the patient demonstrated symptoms and signs consistent with elevated ICP.

Currently, several different treatment regimens for **induction therapy** of cryptococcal meningitis are recommended:

- Irrespective of which regimen is used, patients must be followed carefully in the hospital for at least 7 days and ideally 14 days **(AII).** Lumbar puncture should be performed on Day 7 and Day 14 of treatment to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily lumbar punctures should be performed until the pressure and symptoms are decreased to the normal range **(AII).**

Preferred Regimens

In the United States and other settings where daily monitoring of electrolytes and kidney function and administration of electrolytes and intravenous fluids is possible:

- Liposomal amphotericin B (IV 3–4 mg/kg daily) plus flucytosine (25 mg/kg orally [PO] four times daily) for 2 weeks is the regimen preferred and recommended by the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections Adults and Adolescent With HIV (the Panel) **(AII).**[28,34]

In resource-limited health care settings:

- A single dose of liposomal amphotericin B (IV 10 mg/kg on Day 1) combined with oral flucytosine (25 mg/kg four times daily) and fluconazole (1,200 mg/day) for 2 weeks is the preferred regimen recommended by the World Health Organization **(AI).**[33]

Alternative Regimens

- If amphotericin B lipid complex is the only available lipid amphotericin B formulation available, a dosage of 5 mg/kg IV daily combined with flucytosine 25 mg/kg PO four times daily should be administered for 2 weeks **(BII).** However, there is much less experience with amphotericin B lipid complex than with the liposomal amphotericin B formulation.

- If amphotericin B deoxycholate is the only available formulation of amphotericin B, this can be used at a dosage of 1 mg/kg IV daily combined with flucytosine 25 mg/kg PO four times daily for 1 week, followed by fluconazole 1,200 mg/day PO for an additional week **(BI).**[30]

When using flucytosine, therapeutic drug monitoring should be performed, if available, particularly in patients who have renal impairment. Serum peak concentrations of flucytosine should be obtained 2 hours post dose after three to five doses have been administered. Peak serum concentrations should be between 25 mg/L and 100 mg/L.[17] Renal function should be monitored closely and the flucytosine dose adjusted accordingly for those with renal impairment (see Table 6). For those without access to timely flucytosine concentrations, which is a common occurrence, frequent blood counts and renal functions are needed to detect bone marrow toxicity, especially when renal impairment is present.

The addition of flucytosine to the amphotericin B regimen during acute treatment is associated with more rapid sterilization of CSF and survival benefit.[34-36] For instance, a randomized clinical trial of 299 patients showed that the combination of amphotericin B deoxycholate at a dose of 1 mg/kg daily plus flucytosine was associated with improved survival compared to the same dose of amphotericin B without adjunctive flucytosine.[37] Adjunctive fluconazole 800 to 1,200 mg per day plus amphotericin B has been used in the absence of flucytosine, but flucytosine has a survival advantage over fluconazole and is preferred **(BI)**.[30] Amphotericin B deoxycholate with flucytosine **(BI)** or with fluconazole at a dose of 800 to 1,200 mg per day **(BI)** or liposomal amphotericin B with fluconazole at a dose of 800 to 1,200 mg per day **(BIII)** may be reasonable alternatives in some circumstances.

Fluconazole, administered at 1,200 mg daily **(CIII)** or with flucytosine **(BII),** is a potential all-oral alternative to amphotericin B regimens.[30,38] Based on studies assessing early fungicidal activity, fluconazole alone (1,200 mg/day) is inferior to amphotericin B for induction therapy.[39,40] Therefore, fluconazole is preferably used with flucytosine. Fluconazole alone is recommended only for patients who cannot tolerate other agents or who do not respond to standard treatment, or when other antifungals are not available.

Consolidation Therapy

A lumbar puncture and repeat CSF culture should be performed after 1 week and/or 2 weeks of induction therapy in all patients **(AII).** After 2 weeks of induction therapy, clinically stable patients may be switched to consolidation therapy while awaiting CSF culture results. Successful induction therapy is defined as substantial clinical improvement and a negative CSF culture from the end-of-induction lumbar puncture. India ink and CSF CrAg may remain positive at Week 2 of therapy and are not indicative of failure. Monitoring serum or CSF CrAg titers is of no value in determining initial response to therapy and **is not recommended (AII).**[41,42] If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of lumbar opening pressure and CSF culture, should be performed.

Consolidation therapy should be initiated with fluconazole 800 mg daily for at least 8 weeks after receiving a clinically successful 2 weeks of induction therapy **(AII).** The recommendation to use 800 mg rather than 400 mg fluconazole for consolidation therapy is based on several findings. Early clinical trials that used 400 mg fluconazole for consolidation noted breakthrough infection during consolidation.[27] Fluconazole 400 mg per day provides concentrations in the CSF that are only fungistatic, and other studies showed that the early antifungal activity of fluconazole in CSF of people with cryptococcal meningitis increases linearly with increasing doses of the drug.[37,39] A phase 2 trial of treatment with either 400 mg or 800 mg fluconazole found that relapses were more frequent in people receiving 400 mg fluconazole.[43] In clinically stable people, the dose of fluconazole for consolidation therapy should be 800 mg per day until CSF cultures are known to be sterile and ART is initiated, at which point the dose can be decreased to 400 mg per day **(AII).**[44]

For people who have completed first-line recommended or other regimen(s) as 2-week induction therapy but have not improved clinically or remain clinically unstable, continuation or starting of amphotericin B plus flucytosine is recommended until the CSF fungal cultures are confirmed to be negative **(BIII).** For outpatients who are not ill enough to be hospitalized but still have positive CSF cultures after completing 2 weeks of induction therapy, flucytosine can continue to be administered for an additional 2 weeks with fluconazole at a dose of 1,200 mg daily or fluconazole monotherapy can be administered at 1,200 mg daily **(BIII).** A lumbar puncture should be performed after 4 weeks of induction therapy to confirm that the cultures have become negative; if still positive, another 2-

week liposomal amphotericin B plus flucytosine induction course may be considered. For all people with CSF cultures positive at Week 2, the duration of consolidation therapy should be for 8 weeks from the time the CSF cultures are confirmed as negative.[27,35,45]

Itraconazole 200 mg twice per day can be used as an alternative therapy for consolidation if fluconazole is not available or is not tolerated by an individual patient **(CI),** but it is clearly inferior to fluconazole.[45] Limited data are available for use of the newer triazoles—voriconazole, posaconazole, and isavuconazole—for either consolidation or maintenance therapy for patients with cryptococcosis. Most of the reported data have been on the use of these extended-spectrum triazole antifungals for treatment of refractory cases, with success rates of approximately 50%.[46-48] Currently, the role of posaconazole, voriconazole, and isavuconazole in the initial management of cryptococcosis has not been established, and these agents **are not initially recommended** for consolidation or maintenance therapy **(AIII).** Echinocandins have no clinical activity against *Cryptococcus* spp. and **are not recommended** for the clinical management of cryptococcosis **(AII).**

Maintenance Therapy

Fluconazole 200 mg per day is used for maintenance treatment and continued until at least 1 year from initiation of antifungal therapy and assuming there is some immune reconstitution on ART and the patient is asymptomatic at the end of 1 year **(AI)** (see the Preventing Recurrence section below).[49]

Treatment of Non–Central Nervous System Cryptococcosis and Asymptomatic Antigenemia

Non-CNS extrapulmonary cryptococcosis and diffuse pulmonary disease should be treated the same as CNS disease **(BIII).** For those with mild symptoms and only focal pulmonary infiltrates with negative serum CrAg, treatment with fluconazole 400 mg per day for 6 to 12 months combined with effective ART is recommended **(BIII).** Duration of therapy should be guided by symptom resolution.[22]

All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease.[13,23,50] If the CSF is normal but the serum CrAg titer is ≥1:640 by LFA (or ≥1:160 by EIA or latex agglutination), even in the absence of meningitis, the risk for mortality and/or progression to meningitis increases with fluconazole monotherapy alone, and these patients should be treated the same as patients with cryptococcal meningitis **(BII).**[23]

Whether to sample the CSF to rule out CNS disease in people with isolated, fully asymptomatic cryptococcal antigenemia is dependent on underlying risk, such as advanced immunosuppression and absence of antiretroviral therapy, and the serum CrAg LFA titer. Those at lower risk and with serum CrAg titer <1:80 by LFA (or <1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture, as empiric treatment for meningitis does not improve outcomes **(AI).**[51] All others should undergo CSF sampling to rule out CNS disease. Those with normal CSF, fully asymptomatic cryptococcal antigenemia, and serum CrAg titers <1:640 by LFA (or <1:160 by EIA or latex agglutination) should be treated with fluconazole 800 to 1,200 mg per day for 2 weeks, followed by 400 to 800 mg per day for 10 weeks, followed by 200 mg daily, for a total of 6 months combined with effective ART **(BIII).**[22]

Special Considerations Regarding ART Initiation

Unlike with other opportunistic infections (OIs), ART initiation generally is deferred for 4 to 6 weeks after antifungal agents are started for treatment of CNS cryptococcosis **(AI).** A randomized clinical trial conducted at three sites in Africa compared patients with cryptococcal meningitis who started ART within 1 to 2 weeks (median 9 days) after the diagnosis of meningitis with patients for whom ART was delayed for 4 to 6 weeks (median 36 days) after diagnosis.[52] This clinical trial used amphotericin B deoxycholate 0.7 to 1.0 mg/kg once daily plus fluconazole 800 mg once daily during the induction phase of antifungal treatment. A significantly greater increase in 6-month mortality occurred in the early ART group than in the delayed ART group (45% vs. 30%, $P = 0.03$). This increase was most pronounced during the first 8 to 30 days of the study ($P = 0.007$). The difference in mortality between the early ART group and the delayed ART group was even greater among individuals with CSF white cell count <5 cells/µL ($P = 0.008$). The excess deaths in the early ART group may have been attributable to paradoxical IRIS, although the timing and incidence of IRIS reportedly did not differ between the two groups.[53] In a trial conducted in China, 102 participants with cryptococcal meningitis were randomized to start ART within either 2 to 5 weeks or >5 weeks after starting antifungal therapy; the majority received amphotericin with flucytosine induction therapy. The primary analysis did not demonstrate a statistically significant difference in mortality; however, a smaller secondary analysis of 78 patients demonstrated excess risk of death in the early ART group compared with the deferred group within the window of 5 to 10 weeks after initiation of antifungal treatment.[54] It is not clear that the secondary analysis had adequate statistical power for the comparison, making the overall interpretation of this study complicated. In a recently published retrospective observational cohort study of participants enrolled from high-resourced health care systems in Europe and North America, investigators used marginal structural modeling with category censoring, inverse proportional weighting, and adjustment for bias to simulate a randomized trial of earlier versus later initiation of ART.[53] A total of 630 people with HIV were identified with cryptococcal meningitis from more than 30 cohorts between 1994 and 2012. Participants were eligible for the analyses if at meningitis diagnosis they were older than 16 years and had a CD4 count, a viral load measurement and follow-up laboratory test results, study visits, and outcomes data. Among these, 432 (69%) were considered ineligible due to insufficient outcome data (256; 41%) or missing baseline CD4 or HIV viral load (176; 28%). Among the 190 eligible patients, 145 started ART during treatment for cryptococcal meningitis.[55] The primary analysis for the simulated trial compared initiation of ART within 14 days of cryptococcal meningitis diagnosis versus starting ART within 14 to 56 days of diagnosis. There were 13 deaths in the early ART group and 20 deaths in the delayed ART group, with an adjusted hazard ratio (aHR) of 1.40 (0.66–2.95) for early versus later initiation of ART. The authors concluded that there was little evidence that earlier ART was associated with higher mortality. The incidence of IRIS was not reported.[55,56]

The issue of when to start ART in the setting of cryptococcal meningitis remains controversial. The randomized trials, most of which are more than a decade old, were largely done in low- and middle-income countries where access to currently recommended antifungal treatment, monitoring, and support may have been less optimal, and they demonstrated overall mortality rates substantially higher than had been reported in higher resourced settings. While the observational cohort study in higher resourced settings is limited by its observational, retrospective nature and cannot fully address unrecognized biases, it is unlikely that a suitably powered prospective randomized trial can be done in high-resourced settings now, given the precipitous decline in incidence of cryptococcal meningitis in people with HIV treated with more effective antifungal therapy and more effective and better tolerated ART regimens than were available in some of the earlier trials. Therefore, most experts aim to start ART within 4 weeks of antifungal therapy; however, individual patient factors may allow for

earlier or later initiation of ART. In general, ensuring that the patient's CSF cultures are sterile before starting ART will reduce the risk of IRIS.[57] If ART must be started sooner, the patient should be monitored closely for paradoxical IRIS with a low threshold to intervene (see "Monitoring of Response to Therapy and Adverse Events," below).[55] For non-CNS cryptococcosis, for which the risk of symptomatic IRIS appears to be lower, the optimal time to begin ART after antifungal therapy is less clear. However, in patients with non-CNS cryptococcosis, it is prudent to delay initiation of ART for 2 weeks after starting antifungal therapy **(BIII).**

All of the triazole antifungals have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents. These interactions and recommendations for dosage adjustments, where feasible, are listed in the Drug–Drug Interaction tables in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV.

Monitoring and Management of Response to Therapy and Adverse Events

Elevation of ICP can cause clinical deterioration despite a microbiologic response; complications are more likely to occur if the CSF lumbar opening pressure is ≥25 cm CSF in the lateral decubitus position.[7,27] In a large clinical trial in people with AIDS and cryptococcal meningitis, increased ICP was associated with 92% of deaths during the first 2 weeks of antifungal therapy and 71% of deaths during Weeks 3 to 10.[7] In another clinical trial, people with HIV who received at least one therapeutic lumbar puncture within 7 days after diagnosis (median time of 3 days) had a 69% relative reduction in the risk of death through 11 days, regardless of initial opening pressure.[58] Although it is uncertain which patients with high lumbar opening pressures will experience clinical deterioration, those with symptoms and signs of increased ICP require immediate clinical intervention to reduce ICP.

Control of elevated ICP is critical to reducing acute mortality. Lumbar opening pressure should be measured in all people with cryptococcal meningitis at the time of diagnosis. However, in routine practice, CSF opening pressure frequently is not measured. Among people in whom CSF opening pressure was not measured initially, a repeat lumbar puncture should be performed with measurement of opening pressure. For people with ongoing headaches, a repeat lumbar puncture should be performed with urgency, and among those without headaches, a repeat lumber puncture should be considered strongly within 48 hours of the initial procedure.[58] Measures to decrease ICP should be used for all people with cryptococcal meningitis who have confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs indicative of increased ICP. Drainage of CSF via lumbar puncture is recommended for initial management **(AII).** One approach is to remove a volume of CSF that reduces the opening pressure by at least 50% or normalizes the pressure to <20 cm CSF.[58,59] In the absence of a manometer, removal of 20 to 25 mL of CSF is recommended **(AIII).** Among patients with ongoing symptoms, therapeutic lumbar punctures should be repeated at least daily until symptoms and signs consistently improve and opening pressure normalizes to <20 cm CSF **(AII).** Because a survival benefit is associated with therapeutic lumbar puncture regardless of baseline CSF opening pressure, strong consideration should be given to repeating a therapeutic lumbar puncture within 72 hours of the initial procedure in those who are relatively asymptomatic or who had a baseline CSF opening pressure of <25 cm CSF, because ICP can be a dynamic process that changes over time **(BII).**[58] If the initial opening pressure was not measured, a second lumbar puncture is recommended **(AII).**

CSF shunting through a lumbar drain or ventriculostomy should be considered for people who cannot tolerate repeated lumbar punctures or for those in whom signs and symptoms of increased ICP persist

after multiple lumbar punctures **(BIII).** Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended (AIII).** Acetazolamide **should not be used** as therapy for increased ICP management because it may exacerbate hyperchloremic acidosis from amphotericin B and does not result in a meaningful decrease in ICP **(AI).**[60] A randomized study that compared a 6-week course of a tapering dose of dexamethasone with placebo among 451 Asian and African patients with cryptococcal meningitis found that dexamethasone did not improve survival through 10 weeks, was noted to not be as effective at killing of *Cryptococcus,* and was associated with more adverse events.[61] These data support the recommendation that **corticosteroids should not be used** during induction therapy for ICP control for HIV-associated cryptococcal meningitis unless they are being used for treatment of IRIS **(AI).**

People treated with amphotericin B formulations should be monitored for nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1,000 mL of normal saline reduces the risk of nephrotoxicity during amphotericin B treatment. For people with severe infusion-related adverse reactions, acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered 30 minutes before the infusion to reduce the severity of amphotericin B infusion reactions **(CIII);** meperidine (25–50 mg titrated during infusion) is effective for treating amphotericin B–associated rigors and should be given before each dose daily and after the first incidence of rigors to prevent future rigors **(BII).** Routine use of potassium chloride (40 mEq per day) and magnesium (8 mEq per day) supplementation should be considered because the risk of hypokalemia and hypomagnesemia becomes near universal after 1 week of therapy, regardless of the amphotericin B formulation used **(AII).**[62]

Flucytosine is associated with concentration-dependent bone marrow toxicity. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities. In people receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and can be guided by flucytosine concentrations. Peak serum flucytosine concentrations should be obtained 2 hours after an oral dose; the therapeutic range is between 25 and 100 mg/L. If therapeutic drug monitoring is not possible or kidney dysfunction is not present, frequent complete blood counts with differential (i.e., at least biweekly) can be used to detect cytopenias **(BII).**[30]

Common side effects of higher dose fluconazole therapy can include dry skin (17% of patients) and alopecia (16% of patients).[63] Increased liver transaminases or alkaline phosphatase are relatively rare in fluconazole dosages of 400 to 800 mg, with only 1 to 2% of patients having values >5 times the upper limit of normal.[52] For people who have difficulty tolerating higher fluconazole doses, the consolidation therapy fluconazole dose can be reduced to 400 mg per day after ART initiation. **(BII).**[44]

Immune Reconstitution Inflammatory Syndrome

An estimated 10 to 30% of people with HIV who have cryptococcal meningitis experience IRIS after initiation or reinitiation of effective ART and both unmasking (before start of antifungal therapy) or paradoxical (after start of antifungal therapy) IRIS may occur.[64,65] People with HIV who have cryptococcal IRIS are more likely to be ART naive and those whose CSF has less inflammation on presentation seem to be at higher risk of cryptococcal IRIS.[66] The risk of IRIS can be minimized by achieving CSF culture sterility before starting ART, using fluconazole 800 mg per day as consolidation therapy, and deferring ART initiation for 4 to 6 weeks from the start of antifungal therapy **(AII).**[52,67] Distinguishing paradoxical IRIS from treatment failure with culture-positive relapse is difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite

microbiological evidence of effective antifungal therapy with sterile CSF cultures,[66,68] whereas treatment failure is associated with continued positive cultures. The primary microbiological criterion for treatment failure is a CSF culture that yields *Cryptococcus*, not the visual appearance of yeasts during treatment; the culture may take days to weeks to become positive. A negative PCR test (e.g., BioFire FilmArray Meningitis/Encephalitis Panel) has a high predictive value for sterile CSF cultures and can be diagnostically useful for distinguishing paradoxical IRIS with a negative CSF PCR from culture-positive relapse with a positive CSF PCR.[15]

The appropriate management strategy for IRIS **is to continue both ART and antifungal therapy** and reduce elevated ICP if present **(AII).** While diagnostic tests are pending, escalating antifungal therapy (i.e., restarting amphotericin B therapy or increasing the fluconazole dose to 1,200 mg per day) is recommended **(BIII).** In people with severe symptoms of IRIS, some experts recommend a brief course of tapering doses of corticosteroids. Dosages have varied but commonly start at 1.0 mg/kg per day of prednisone; precise data-driven management strategies have not been developed. Serum C–reactive protein (CRP) is generally elevated at the time IRIS develops;[69] CRP will decrease with corticosteroid therapy if IRIS is present and can be used to empirically monitor IRIS resolution. Once clinical improvement is evident, it is recommended that fluconazole at consolidation therapy doses should be continued or restarted upon hospital discharge **(BIII).**

The risk of IRIS appears to be much lower and the syndrome seems to be less severe with other forms of cryptococcosis—such as lymphadenitis, cutaneous abscesses, and bony lesions—than with cryptococcal meningitis.[70] Management of IRIS with other forms of cryptococcosis is similar to that for IRIS associated with cryptococcal meningitis, including continuing ART, initiating or continuing antifungal therapy **(AIII),** and only considering the use of corticosteroids if clinical symptoms are severe **(CIII).**

Managing Treatment Failure

Treatment failure is defined as (1) a lack of clinical improvement and continued positive cultures after 2 weeks of appropriate therapy that has included management of increased ICP, or (2) relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥4 weeks of treatment. Primary fluconazole resistance in *Cryptococcus* isolates has been reported in the United States but is uncommon.[71] Therefore, susceptibility testing is not recommended routinely for initial management of cryptococcosis. However, if treatment failure or relapse occurs, *Cryptococcus* isolates should undergo antifungal susceptibility testing. Robust clinical data are lacking, but strains of *Cryptococcus* with fluconazole minimum inhibitory concentrations (MIC) ≥16 µg/mL are considered not fully susceptible.[72,73]

Optimal therapy for patients with treatment failure has not been established. If treatment failure occurs after induction with alternative regimens, preferred regimens should be started. Furthermore, those initially treated with an amphotericin B formulation should remain on this agent until clinical response occurs. In this setting, liposomal amphotericin B (3–6 mg/kg daily) or amphotericin B lipid complex (5 mg/kg daily) is better tolerated and has greater efficacy than the deoxycholate formulation[28,74,75] and should be considered when initial treatment with other regimens fails **(AII).**

In the setting of treatment failure or relapse, verifying CSF culture sterility at the completion of re-induction therapy is critical **(AIII).** After CSF sterility is achieved, outpatient consolidation therapy should consist of fluconazole at a higher dose of 1,200 mg per day and optimization of ART. For *Cryptococcus* with decreased azole-susceptibility (i.e., ≥16 µg/mL MIC for fluconazole), adjunctive

weekly amphotericin B administration during consolidation therapy may be considered **(BIII).**[73] Higher doses of fluconazole (i.e., 1,200 mg per day) in combination with flucytosine 25 mg/kg four times per day also may be considered **(BI).** The newer triazoles—posaconazole, voriconazole, and isavuconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy,[46-48] but they offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates only high-level fluconazole resistance. Most clinical failures are not due to antifungal drug resistance but rather result from inadequate induction therapy, nonadherence, drug-drug interactions that decrease the serum concentrations of fluconazole (e.g., with rifampin), or the development of paradoxical IRIS. Failures also may occur with high fungal burden disease and/or severe immunosuppression of host.

Preventing Recurrence

When to Start Maintenance Therapy

People who have completed 10 weeks of induction and consolidation therapy for cryptococcal meningitis or disseminated cryptococcosis should be treated with chronic maintenance or suppressive therapy with fluconazole 200 mg per day for at least 1 year **(AI).** Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease and should generally not be considered **(CI).**[45 73] For people in whom susceptibility studies have been performed and the fluconazole MIC is ≥16 µg/mL, the fluconazole dose may be increased to 400 mg per day **(BIII).** Failure to administer this secondary prophylaxis for an entire year is the most common reason for subsequent relapse of cryptococcal disease.[76]

When to Stop Maintenance Therapy

Data evaluating relapse after successful antifungal therapy for cryptococcosis and discontinuation of maintenance therapy while on ART are limited. In a European study, recurrences of cryptococcosis were not found among 39 participants on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 count was 297 cells/mm^3, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[77] A prospective randomized study of 60 people in Thailand documented no recurrences of cryptococcosis during 48 weeks of follow-up among 22 patients whose antifungal therapy was discontinued after reaching a CD4 count >100 cells/mm^3 with a sustained undetectable HIV RNA level for 3 months on potent ART.[78] Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated OIs, it is reasonable to discontinue maintenance therapy after at least 1 year from initiation of antifungal therapy in people whose CD4 counts are ≥100 cells/mm^3 with undetectable viral loads on ART **(BII).**[79] Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/mm^3 **(AIII).**

Special Considerations During Pregnancy

The diagnosis of cryptococcal infections in pregnant individuals is the same as that in individuals who are not pregnant. Treatment should be initiated promptly after a diagnosis is confirmed, with attention to management of increased ICP. During the postpartum period, anti-inflammatory responses in pregnancy (enhancement of Th2 and suppression of Th1 cytokines) are reversed and may lead to overt clinical manifestations of a previously asymptomatic cryptococcal infection resembling IRIS.[80-82] Close collaboration between obstetric and infectious disease experts is recommended. With CNS cryptococcal infection, the recommendation in nonpregnant individuals is

to defer ART initiation for 4 to 6 weeks after antifungal agents are started to reduce the risk of IRIS; in pregnancy, however, starting ART as expeditiously as possible is associated with lower risk of perinatal transmission of HIV. In the presence of CNS cryptococcal infection, decisions about the timing of ART initiation should be made after consultation with the pregnant person, maternal-fetal medicine specialists, and infectious disease specialists. If ART is started sooner than generally recommended in nonpregnant individuals, close monitoring for IRIS should be implemented with a low threshold for treatment for IRIS. For pregnant people with non-CNS cryptococcosis, the risk of IRIS appears to be lower, and a delay in ART initiation of no longer than 2 weeks after starting antifungal therapy is recommended.

Extensive clinical experience with amphotericin B deoxycholate has not been associated with teratogenicity, and this remains a preferred therapy for cryptococcosis in the first trimester of pregnancy **(AIII).** Although there is less experience in pregnancy with lipid formulations of amphotericin B, these products have been associated with less nephrotoxicity and electrolyte abnormalities than amphotericin B deoxycholate and are an alternative as a preferred therapy for the initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis in pregnant people **(AIII).** Optimal dosing of liposomal amphotericin B in pregnancy is unknown. A recent review of dosing strategies in pregnancy recommended use of ideal body weight rather than total body weight to minimize risk of adverse effects to the fetus while maintaining efficacy **(BII).**[83] Neonates born to women on chronic amphotericin B at delivery may be at increased risk for renal toxicity and electrolyte abnormalities and should be appropriately evaluated as newborns.[84]

Flucytosine use should be considered only when the benefits outweigh the risks to the pregnant person and fetus and should be delayed until after the first trimester when feasible **(AIII).** In animal studies, flucytosine is teratogenic and may be associated with cleft palate and other bone abnormalities. Flucytosine use in pregnancy is limited to case reports and small series, although normal outcomes have been described.[85-87]

In general, azole antifungals **should be avoided** during the first trimester of pregnancy unless the benefit outweighs the risk **(BIII).** Fluconazole has teratogenic potential in the first trimester. Congenital malformations similar to those observed in animals exposed to the drug—including craniofacial and limb abnormalities—have been reported in infants born to mothers who received fluconazole at doses of ≥400 mg per day throughout or beyond the first trimester of pregnancy.[88] Furthermore, animal data suggest that moderate alcohol consumption during pregnancy may increase the potency of fluconazole, resulting in increased risk of craniofacial defects.[89]

Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short-term exposure. A recent meta-analysis describing birth defects in infants exposed to fluconazole during the first trimester evaluated nine cohort, case-control or randomized controlled studies, including 53,407 fluconazole-exposed pregnant people and 3,319,353 unexposed pregnant individuals.[90] Maternal exposure to fluconazole was correlated with an increased prevalence of heart defects in infants for both low dose (≤150 mg) (odds ratio [OR] 1.95; 95% CI, 1.18–3.21; $P = 0.01$) or any dose (OR 1.79; 95% CI, 1.18–2.71; $P = 0.01$). No association was found between either low- or high-dose fluconazole exposure and orofacial, CNS, genitourinary, musculoskeletal, or gastrointestinal defects.[91] One registry-based cohort study[92] of 7,352 women reported a threefold increase in incidence of Tetralogy of Fallot, and a large population-based case-control study[93] specifically noted an increase in transposition of the great arteries (OR 7.56, 95% CI, 1.22–35.45). The latter study also suggested an increase in cleft lip with cleft palate (OR 5.53; 95% CI,

1.68–18.24). In three nested case-control studies using data from the Quebec Prescription Drug Insurance database, there was an increased prevalence of cardiac septal closure anomalies for maternal fluconazole doses greater than 150 mg during pregnancy (OR 1.81; 95% CI, 1.04–3.14).[94] A recent population-based cohort study (included in the meta-analysis) of 1,969,954 pregnancies, including 37,650 pregnancies exposed to fluconazole, found an increased risk of musculoskeletal malformations following exposure to fluconazole during the first trimester of pregnancy (risk of 52.1 per 10,000 pregnancies exposed to fluconazole versus 37.3 per 10,000 pregnancies exposed to topical azoles).[95]

A nationwide cohort study in Denmark[96] found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies (n = 16,561, HR, 1.48; 95% CI, 1.23–1.77) or those with topical azole exposure only (n = 5,646, HR 1.62; 95% CI, 1.26–2.07). Similarly, the nested case-control studies in Canada (n = 320, 868 pregnancies) found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies, and that risk was greater with higher dose of fluconazole exposure (adjusted odds ratio [aOR] with ≤150 mg 2.23, 95% CI, 1.96–2.54; aOR with >150 mg 3.20; 95% CI, 2.73–3.75).[94] However, a cohort study using Swedish and Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use during pregnancy and risk of stillbirth or neonatal death.[97] The meta-analysis noted above also found no association between fluconazole exposure and risk of abortion or stillbirth.[90] Most of the studies regarding effects of fluconazole during pregnancy have involved low doses of the drug and short-term exposure.

On the basis of reported birth defects, the use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh the risks **(CIII).** For pregnant people, amphotericin B should be continued throughout the first trimester if possible **(AIII).** After the first trimester, switching to oral fluconazole may be considered if appropriate clinically for consolidation or maintenance therapy **(CIII).**

Although there have been case reports of birth defects in infants exposed to itraconazole, a recent systematic review and meta-analysis of four cohort studies involving 971,450 pregnant women with 1,311 exposures, found no significant difference in the overall risk of birth defects between those with maternal exposure to itraconazole and those not exposed.[98] While limb and congenital heart defects were the most common defects seen, they were within the rates of the defects published by EUROCAT (the European network of population-based registries for epidemiological surveillance of congenital anomalies). However, the rate of eye defects was higher than that published by EUROCAT. There was no difference in the rates of spontaneous abortion or stillbirth from itraconazole exposure.

Voriconazole (at doses lower than recommended human doses), posaconazole, and isavuconazole are teratogenic and embryotoxic in animals; no adequately controlled studies have assessed their teratogenicity and embryotoxicity in humans. Voriconazole, posaconazole, and isavuconazole **are not recommended** for use during pregnancy, especially in the first trimester **(CIII).**

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Cryptosporidiosis

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Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infects the small bowel mucosa, and, if symptomatic, the infection typically causes diarrhea. *Cryptosporidium* can also infect other gastrointestinal and extraintestinal sites, especially in individuals whose immune systems are suppressed. Advanced immunosuppression—typically CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis.[1] The three species that most commonly infect humans are *C. hominis*, *C. parvum*, and *C. meleagridis*. Infections are usually caused by one species, but a mixed infection is possible.[2,3]

Cryptosporidiosis remains a common cause of chronic diarrhea in people with HIV and AIDS in low- and middle-income countries.[4] In high-income countries with low rates of environmental contamination and widespread availability of potent antiretroviral therapy (ART), the incidence of cryptosporidiosis in people with HIV has decreased. In the United States, the incidence of cryptosporidiosis in people with HIV is now <1 case per 1,000 person-years.[5]

Infection occurs through ingestion of *Cryptosporidium* oocysts. Viable oocysts in feces can be transmitted directly through contact with humans or animals infected with *Cryptosporidium*, particularly those with diarrhea. *Cryptosporidium* oocysts can contaminate public water supplies and recreational water sources—such as swimming pools and lakes—and may persist despite standard chlorination. Person-to-person transmission of *Cryptosporidium* is common, especially among sexually active men who have sex with men.

Clinical Manifestations

Patients with cryptosporidiosis most commonly present with acute or subacute onset of watery diarrhea, which may be accompanied by nausea, vomiting, and lower abdominal cramping. Disease severity can range from asymptomatic to profuse, watery, voluminous diarrhea.[6] More severe symptoms tend to occur in immunosuppressed people, whereas transient diarrhea alone is typical in people with competent immune systems. Fever is present in approximately one-third of patients, and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with *Cryptosporidium,* leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among people with prolonged disease and low CD4 counts.[7] Pulmonary *Cryptosporidium* infections also have been reported and may be under-recognized.[8,9]

Diagnosis

Diagnosis of cryptosporidiosis was traditionally made by microscopic identification of the oocysts in stool with acid-fast staining or direct immunofluorescence, which offers higher sensitivity.[10] Concentration methods (e.g., formalin-ethyl acetate) may facilitate diagnosis of cryptosporidiosis. However, these methods are insensitive, and other diagnostic methods are being increasingly used. Antigen detection by enzyme-linked immunosorbent assay or immunochromatographic tests also is

useful; depending on the specific test, sensitivities reportedly range from 66% to 100%. However, some immunochromatographic tests produce frequent false-positive results.[11] Polymerase chain reaction and multiplex molecular methods are increasingly used for diagnosis and can identify a greater number of cases than microscopic methods.[10,12] Cryptosporidial enteritis also can be diagnosed from small sections of tissue from intestinal biopsy.

A single stool specimen is usually adequate to diagnose cryptosporidiosis in individuals with profuse diarrheal illness, whereas repeat stool sampling is recommended for those with milder disease.

Preventing Exposure

People with HIV should be educated and counseled about how *Cryptosporidium* can be transmitted **(BIII).** Modes of transmission include direct contact with animals and people, including diapered children, infected with *Cryptosporidium*; swallowing contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Scrupulous handwashing can reduce the risk of diarrhea, including diarrhea caused by *Cryptosporidium,* in individuals with HIV.[13] People with HIV should be advised to wash their hands after potential contact with human feces (including after diapering small children). Handwashing also should be recommended in association with the following activities: after handling pets or other animals, after gardening or any other contact with soil, before preparing food or eating, and before and after sex **(BIII).** Individuals with HIV should avoid unprotected sex, especially practices that could lead to direct (e.g., oral-anal sex) or indirect (e.g., penile-anal sex) contact with feces. They should be advised to use prophylactic barrier methods—such as condoms and dental dams—during sex to reduce such exposures **(BIII).**

People with HIV—particularly those with CD4 counts <200 cells/mm^3—should avoid direct contact with diarrhea or stool from pets **(BIII).** They should wear gloves when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII).** People with HIV should also limit or avoid direct exposure to calves and lambs **(BII).** Paying attention to hygiene and avoiding direct contact with stool are important when visiting farms or petting zoos or other premises where animals are housed or exhibited.

People with HIV should not drink water directly from lakes or rivers **(AIII).** Waterborne infection also can result from swallowing water during recreational activities. Individuals with HIV should be cautioned that lakes, rivers, saltwater beaches, some swimming pools, recreational water parks, and ornamental water fountains may be contaminated with human or animal waste that contains *Cryptosporidium. Cryptosporidium* oocysts are extremely chlorine resistant and thus may persist even in chlorinated recreational water.[14,15] They should avoid swimming in water that is likely contaminated and should avoid swallowing water while swimming or playing in recreational water **(BIII).**

Outbreaks of cryptosporidiosis have been linked to drinking water from municipal water supplies. During outbreaks or in other situations in which a community boil water advisory is issued, boiling water for at least 1 minute will eliminate the risk for cryptosporidiosis **(AIII).** Using submicron personal-use water filters (home or office types) or bottled water also may reduce the risk of infection from water from a municipal source or a well **(BII).**

For people with low CD4 counts, the magnitude of the risk of acquiring cryptosporidiosis from drinking water in a non-outbreak setting is uncertain but is likely small. Available data are inadequate to recommend that all people with HIV boil water or avoid drinking tap water in non-outbreak settings. However, people with HIV may consider drinking only filtered water **(CIII),** despite the complexities involved in selecting appropriate water filters, the lack of enforceable standards for removal of *Cryptosporidium* oocysts, the costs of the products, and the difficulty of using the products consistently. Note that ice made from contaminated tap water also can be a source of infection.

People with HIV with low CD4 counts should be cautious about eating raw oysters because cryptosporidial oocysts can survive in oysters for >2 months and have been found in oysters harvested from certain commercial oyster beds **(CIII).** In the hospital setting, standard precautions for use of gloves and for handwashing after removal of gloves should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible individual with HIV **(BIII).** Because of the potential for fomite transmission, some specialists recommend that people with HIV, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis **(CIII).**

People with HIV who travel to low- and middle-income countries should be warned to avoid drinking tap water or using tap water to brush their teeth **(BIII).** They should also avoid using ice that is not made from bottled water and consuming raw fruits or vegetables that may have been washed in tap water **(BIII).**

People with HIV also should avoid other sources of *Cryptosporidium* oocysts as much as possible **(BIII).** This includes avoiding directly working with people with diarrhea; with farm animals, such as cattle and sheep; and with domestic pets that are very young or have diarrhea. If exposure is unavoidable, gloves should be worn and good hand hygiene observed.

Preventing Disease

Recommendations for Preventing Cryptosporidiosis
Preventing Chronic Cryptosporidiosis   • Because chronic cryptosporidiosis occurs primarily in people with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease **(AII)**.

Key: ART = antiretroviral therapy

Because chronic cryptosporidiosis occurs primarily in people with HIV with advanced immunodeficiency, initiation of ART before they become severely immunosuppressed should prevent the disease **(AII).** Rifabutin and possibly clarithromycin taken for *Mycobacterium avium* complex prophylaxis have been found to protect against cryptosporidiosis.[16,17] Rifaximin, which is used for prevention of traveler's diarrhea, also has been used to treat cryptosporidial diarrhea. However, it is unclear whether rifaximin can protect against cryptosporidiosis.[18] Data are insufficient, however, to warrant a recommendation to use rifaximin, rifabutin, or clarithromycin as chemoprophylaxis for cryptosporidiosis.

Treating Disease

Recommendations for Treating Cryptosporidiosis
Managing Cryptosporidiosis
• Preferred Management Strategies
o Aggressive oral and/or IV rehydration and replacement of electrolyte loss **(AIII)**, *and*
o Symptomatic treatment of diarrhea with antimotility agents **(AIII)**; tincture of opium may be more effective than loperamide **(CIII)**.
o People with HIV not taking ART should initiate ART to achieve immune restoration to CD4 count >100 cells/mm^3 **(AII)**.
• General Considerations
o Nitazoxanide 500 mg to 1,000 mg PO twice daily with food for at least 14 days **(CIII)** plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, *or*
o Paromomycin 500 mg PO four times a day for at least 14 days to 21 days **(CIII)** plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement
Pregnancy Considerations
• Rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis during pregnancy, as they are in nonpregnant people **(AII)**.
• Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium **is not recommended** in late pregnancy **(AIII)**.
• Loperamide is the preferred antimotility agent in late pregnancy **(CIII)**. Loperamide should be avoided in the first trimester unless benefits are felt to outweigh potential risks **(CIII)**.
• Nitazoxanide **(CIII)** and paromomycin **(CIII)** can be used in pregnancy after the first trimester.
Other Considerations
• Because diarrhea can cause lactase deficiency, people with cryptosporidiosis should avoid milk products **(CIII)**.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; IV = intravenous; PO = orally

In the setting of severe immune suppression, ART with immune restoration to a CD4 count >100 cells/mm^3 usually leads to resolution of clinical cryptosporidiosis[19-22] and is the mainstay of treatment. People with HIV not already taking antiretrovirals who develop cryptosporidiosis should be started on ART as part of the initial management of cryptosporidiosis **(AII).** Management should also include symptomatic treatment of diarrhea with antimotility agents **(AIII).** Tincture of opium may be more effective than loperamide **(CIII).** Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved to treat secreting tumor–induced diarrhea, is no more effective than other oral antidiarrheal agents and **is usually not recommended (CII).**[23] Because diarrhea can cause lactase deficiency, people with HIV and cryptosporidiosis should avoid milk products **(CIII).**

Rehydration and repletion of electrolyte losses by either oral or intravenous route are important. Stool volume in patients with HIV and AIDS with severe diarrhea can exceed 10 L/day; managing the diarrhea often requires intensive support. Oral rehydration should be pursued aggressively with

oral rehydration solutions **(AIII).** Most patients can be treated with enteral nutrition; total parenteral nutrition is rarely indicated **(CIII).**

Patients with biliary tract involvement may require endoscopic retrograde cholangiopancreatography for diagnosis. They may also benefit from sphincterotomy, stenting, or both.[7,24]

Several agents—including nitazoxanide, paromomycin, clofazimine, and spiramycin—have been investigated in small, randomized controlled clinical trials of adults with HIV.[25] No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.[26]

Nitazoxanide is an orally administered nitrothiazole benzamide with *in vivo* activity against a broad range of helminths, bacteria, and protozoa. Nitazoxanide is approved by the U.S. Food and Drug Administration for treatment of cryptosporidiosis in children over 1 year of age and adults. Nitazoxanide 500 mg administered twice daily for 3 days to adults without HIV but with cryptosporidiosis resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.[27,28] In one study, adults with HIV with cryptosporidiosis and CD4 counts >50 cells/mm^3 were treated with nitazoxanide 500 mg to 1,000 mg twice daily for 14 days; the nitazoxanide treatment group had substantially higher rates of parasitological cure and resolution of diarrhea than the placebo group.[29] Efficacy of nitazoxanide for the treatment of cryptosporidial diarrhea in children with HIV, however, was not confirmed in two randomized trials in children.[30,31] Data from a compassionate use program before the advent of potent ART, which included primarily white male adults with median CD4 counts <50 cells/mm^3, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment.[32] Adverse events associated with nitazoxanide are typically mild, and no important drug–drug interactions have been reported. Because of the clinical significance of cryptosporidiosis, many experts will institute a trial of nitazoxanide or paromomycin in conjunction with ART but never instead of ART **(CIII).**

Paromomycin is a nonabsorbable aminoglycoside indicated for the treatment of intestinal amebiasis but not specifically approved for cryptosporidiosis. Paromomycin in high doses is effective for the treatment of cryptosporidiosis in animal models. A meta-analysis of 11 published studies of paromomycin in humans reported a response rate of 67%; however, there were few cures, relapses were common, and long-term success rates were only 33%.[24] Two randomized trials comparing paromomycin with placebo demonstrated limited effectiveness of the drug among patients with AIDS and cryptosporidiosis.[33,34] One case series suggested a better response rate in patients receiving paromomycin along with ART.[35] Paromomycin may be used instead of nitazoxanide in conjunction with ART but never instead of ART **(CIII).**

Special Considerations with Regard to Starting ART

As noted above, patients with cryptosporidiosis should be offered ART as part of the initial management of cryptosporidiosis **(AII).** In animal and *in vitro* models, HIV protease inhibitors (PI) can inhibit *Cryptosporidium*, but there is no clinical evidence that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII).**[36,37]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored closely for signs and symptoms of volume depletion, electrolyte imbalance, weight loss, and malnutrition. Immune reconstitution inflammatory syndrome (IRIS) has been described in association with three cases of extraintestinal cryptosporidiosis.[38]

Managing Treatment Failure

Supportive treatment and optimization of ART to achieve full virologic suppression are the main approaches to managing treatment failure **(AIII).** The clinical response rather than results of stool tests should be used to guide the response to therapy. Some authorities advocate adding antiparasitic drugs **(CIII),** such as nitazoxanide or paromomycin alone or in combination with azithromycin, as well as optimizing ART in patients with treatment failure and cryptosporidiosis.[39,40]

Preventing Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations During Pregnancy

Rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis during pregnancy, as they are in nonpregnant people **(AII).** Pregnancy should not preclude the use of ART and, in fact, is always an indication for ART. Nitazoxanide is not teratogenic in animals, but no data on use in human pregnancy are available. Nitazoxanide can be used in pregnancy after the first trimester in people with severe symptoms **(CIII).** Limited information is available about the teratogenic potential of paromomycin, but oral administration is associated with minimal systemic absorption, which may minimize potential risk. Paromomycin can be used in pregnancy after the first trimester in people with severe symptoms **(CIII).** Loperamide is poorly absorbed and has not been associated with birth defects in animal studies. However, one study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.[41] Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII).** Loperamide is the preferred antimotility agent in late pregnancy **(CIII).** Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium **is not recommended** in late pregnancy **(AIII).**[42]

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Cystoisosporiasis (Formerly Isosporiasis) (Last updated September 10, 2015; last reviewed January 10, 2024)

Epidemiology

Isosporiasis, also known as cystoisosporiasis, occurs worldwide but predominantly in tropical and subtropical regions. Immunocompromised patients, including those who are HIV-infected, are at increased risk for chronic, debilitating illness.[1-7] Although *Isospora (Cystoisospora) belli* completes its life cycle in humans, the oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective. On the basis of limited data, the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.[2] Infection results from ingestion of sporulated oocysts, such as from contaminated food or water. After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.

Clinical Manifestations

The most common manifestation is watery, non-bloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, particularly in immunocompromised patients, resulting in severe dehydration, electrolyte abnormalities such as hypokalemia, weight loss, and malabsorption.[6-12] Acalculous cholecystitis/cholangiopathy[2,13-15] and reactive arthritis[16] also have been reported.

Diagnosis

Typically, infection is diagnosed by detecting *Isospora* oocysts (dimensions, 23–36 µm by 12–17 µm) in fecal specimens.[2] Oocysts may be shed intermittently and at low levels, even by patients with profuse diarrhea. Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-fast techniques, on which oocysts stain bright red, and UV fluorescence microscopy, under which they autofluoresce.[2,17] Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens.[2,10] Extraintestinal infection, such as in the biliary tract, lymph nodes, spleen, and liver, has been documented in postmortem examinations of HIV-infected patients.[2,18-20]

Preventing Exposure

Because *I. belli* is acquired by ingesting infected water or food, avoiding potentially contaminated food or water in isosporiasis-endemic areas may help prevent infection.

Preventing Disease

In some settings, chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis.[1,3,4,21] In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).[1] In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm³.[3] After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a Los Angeles county AIDS surveillance registry during the pre-ART era, the prevalence of isosporiasis was lower in patients with versus without a history of Pneumocystis pneumonia—indirect evidence of a protective effect from use of TMP-SMX for Pneumocystis pneumonia.[4] Insufficient evidence is available, however, to support a general recommendation for primary prophylaxis for isosporiasis per se, especially for U.S. travelers in isosporiasis-endemic areas.

Treating Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients **(AIII)**. TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis **(AI)**. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails **(AIII)**.

Three studies in HIV-infected patients in Haiti have demonstrated the effectiveness of various treatment regimens of TMP-SMX.[6,7,22] The patients were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not specified. On the basis of the initial studies,[6,7] the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily **(AII)**.[23] In another study, TMP-SMX (160/800 mg) administered twice daily was also effective **(BI)**.[22] Although published experience using two daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and the duration of therapy (up to 3–4 weeks)[6,10] if symptoms worsen or persist **(BIII)**. Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.[2,9,10,24-26] However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the United States **(CIII)**; it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,[27] and pyrimethamine and sulfadoxine clear slowly from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis.[3,28,29] Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients **(BIII)**.

The author panel has issued a statement on the availability of pyrimethamine. For more information, please visit https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine.

Special Considerations with Regard to Starting ART

Only limited data address the utility of ART in the setting of *Isospora* and HIV co-infection.[3,14,21] Immune reconstitution with ART may result in fewer relapses of isosporiasis, and no cases of immune reconstitution inflammatory syndrome (IRIS) have been reported. Therefore, the potential benefits of ART likely outweigh the risks. For patients with isosporiasis who otherwise fulfill criteria for ART, TMP-SMX therapy and ART can be started simultaneously; there is no known reason to defer initiation of ART other than the potential for poor ART absorption **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored for clinical response and adverse events. In HIV-infected patients, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, and elevated transaminase levels. IRIS has not been described.

Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered. Ciprofloxacin is a second-line agent **(CI)**. On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but may have modest activity against *I. belli*.[22]

Unsubstantiated or mixed data are available for albendazole,[29-31] nitazoxanide,[32,33] doxycycline,[34] the macrolides roxithromycin and spiramycin,[25,35,36] and the veterinary anticoccidial agent diclazuril **(CIII)**.[37,38] Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective.[8,25,26,28,35,37] Apparent or partial responses, if noted, may be attributable to treatment of concomitant infections or to nonspecific effects.

Preventing Recurrence

Patients with CD4 cell counts <200 cells/mm^3 should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections **(AI)**. In studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk of relapse.[6,7,22] In a randomized, placebo-controlled trial, no symptomatic recurrences were noted in patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) **(AI)**.[7] Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1600 mg) have been effective **(BIII)**;[5,10] however, clinical and parasitologic relapses despite maintenance TMP-SMX therapy and ART have been reported.[14]

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used **(BIII)**.[28] On the basis of limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative **(CI)**.[22]

When To Stop Secondary Prophylaxis

The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm^3 for >6 months after initiation of ART **(BIII)**.

Special Considerations During Pregnancy

TMP-SMX is the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is in persons who are not pregnant. Although first-trimester exposure to trimethoprim has been associated with a small increased risk of birth defects,[39-42] TMP-SMX therapy should be provided in the setting of maternal symptomatic *I. belli* infection. Because of concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection **(CIII)**. Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.[43] Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.[44]

Recommendations for Treating *Isospora belli* Infection

Treating *Isospora belli* Infection
General Management Considerations:
• Fluid and electrolyte support in patients with dehydration **(AIII)**
• Nutritional supplementation for malnourished patients **(AIII)**
Preferred Therapy for Acute Infection:
• TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days **(AII)**, *or*
• TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days **(BI)**
• One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist **(BIII)**
• IV therapy for patients with potential or documented malabsorption
Alternative Therapy For Acute Infection (For Patients with Sulfa Intolerance):
• Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily **(BIII)**, *or*
• Ciprofloxacin 500 mg PO BID for 7 days **(CI)**
Chronic Maintenance Therapy (Secondary Prophylaxis)
(In Patients with CD4 Count <200/mm^3)
Preferred Therapy:
• TMP-SMX (160 mg/800 mg) PO 3 times weekly **(AI)**
Alternative Therapy:
• TMP-SMX (160 mg/800 mg) PO daily **(BIII)**, *or*
• TMP-SMX (320 mg/1600 mg) PO 3 times weekly **(BIII)**, *or*
• Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily **(BIII)**
• Ciprofloxacin 500 mg PO 3 times weekly **(CI)** as a second line alternative
Criteria for Discontinuation of Chronic Maintenance Therapy
• Sustained increase in CD4 count >200 cells/mm^3 for >6 months in response to ART and without evidence of active *I. belli* infection **(BIII)**

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole

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Cytomegalovirus Disease (Last updated July 1, 2021; last reviewed January 10, 2024)

Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpesvirus family that can cause disseminated or localized end-organ disease in people with HIV with advanced immunosuppression. Most clinical disease occurs in individuals previously infected with CMV experiencing reactivation of latent infection. Infection with a novel strain also may occur.

End-organ disease caused by CMV occurs in patients with HIV and advanced immunosuppression, typically those with CD4+ T lymphocyte cell (CD4) counts <50 cells/mm^3 who are not receiving, adherent to, or responding to antiretroviral therapy (ART).[1–3] Among those treated with ART who have achieved virologic control, a new diagnosis of CMV end-organ disease is exceedingly rare.

Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis, the most common CMV end-organ disease in such patients.[1–3] The incidence of new cases of CMV end-organ disease has declined by ≥95% with the advent of potent ART.[4,5] For those with established CMV retinitis, recurrence of active lesions occurs at a rate substantially lower than that seen in the era before potent ART. Nevertheless, even for those with immune recovery sufficient to warrant discontinuation of anti-CMV therapy (i.e., CD4+ counts >100 cells/mm^3) relapse of the retinitis occurs at a rate of 0.03/person-year and has been documented[6] at CD4 counts as high as 1,250 cells/mm^3. Therefore, regardless of whether or not anti-CMV therapy is continued, regular ophthalmologic follow-up is needed.

Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease in people with HIV. It occurs as unilateral disease in two-thirds of patients at presentation, but disease ultimately progresses to bilateral in most patients in the absence of therapy or immune recovery.[6] In patients with unilateral CMV retinitis and CD4 count <50 cells/mm^3, rates of contralateral disease approach those of the prepotent ART era.[6]

Peripheral retinitis (i.e., outside the major vascular arcades, not involving the macula or optic disc) may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Posterior retinal lesions, especially those impinging on the macula or optic disc, are associated with decreased visual acuity or central visual field defects. CMV retinitis is a full-thickness necrotizing retinal infection. The characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage. The most typical feature is the lesion border, which has tiny dry-appearing, granular, dot-like "satellites" at the interface between infected and normal retina. There will be little inflammation of the vitreous humor unless immune recovery with ART occurs.[1] Blood vessels near the lesions may appear to be sheathed. Occasionally, CMV retinitis lesions, particularly peripheral lesions, may have only a granular appearance throughout the lesion.

In the absence of effective ART or specific anti-CMV therapy, retinitis lesions invariably enlarge. Untreated lesions in severely immunodeficient individuals will involve the entire retina over a period of no longer than 6 months. Movement of lesion borders occurs at variable rates in different directions,[7] causing a characteristic "brushfire" pattern, with their granular, leading edges advancing before an atrophic gliotic scar.[8]

Colitis occurs in 5% to 10% of patients with AIDS and CMV end-organ disease.[2] The most frequent clinical manifestations are weight loss, fever, anorexia, abdominal pain, diarrhea, and malaise. In the colon, and especially in the cecum, CMV can cause perforation and present as an acute abdomen. Computed tomography may show colonic thickening or a colonic mass that may be mistaken for malignancy or other opportunistic infections (OI). Hemorrhage and perforation can be life-threatening complications.

Esophagitis occurs in a small percentage of patients with AIDS who experience CMV end-organ disease and causes odynophagia, nausea, and occasionally midepigastric or retrosternal discomfort as well as fever.

CMV pneumonitis is uncommon in people with HIV, which is in contrast to other conditions with severe immunosuppression, such as solid organ and stem-cell transplant patients. CMV is detected frequently in the bronchoalveolar lavage (BAL) using DNA–specific polymerase chain reaction (PCR), but is a bystander most of the time and should trigger a search for a more likely causative pathogen. CMV PCR from the BAL has not been shown to have diagnostic value in people with HIV.

CMV neurologic disease includes dementia, ventriculoencephalitis, and polyradiculomyelopathies.[9] Patients with dementia caused by CMV encephalitis typically have lethargy or confusion in the presence or absence of fever. Cerebrospinal fluid (CSF) typically demonstrates lymphocytic pleocytosis, low-to-normal glucose levels, and normal-to-elevated protein levels, although normal CSF findings do not rule out the diagnosis of CMV encephalitis. Patients with ventriculoencephalitis have a more acute course, with focal neurologic signs, often including cranial nerve palsies or nystagmus, and rapid progression to death. Periventricular enhancement of computed tomography or magnetic resonance images is highly suggestive of CMV ventriculoencephalitis, rather than HIV-associated neurocognitive disorder. CMV polyradiculomyelopathy or transverse myelitis causes a Guillain-Barre-like syndrome characterized by radicular back pain, urinary retention, and progressive bilateral leg weakness. Clinical symptoms usually progress over several weeks to include loss of bowel and bladder control and flaccid paraplegia. A spastic myelopathy has been reported, and sacral paresthesia can occur. The CSF in CMV polyradiculopathy usually demonstrates neutrophilic pleocytosis (usually 100 to 200 neutrophils/μL and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

Diagnosis

The diagnosis of CMV end-organ disease is typically made on the basis of the clinical presentation and, when possible, evidence of the virus in tissue. CMV retinitis usually is diagnosed based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. Diagnosis in that setting has a 95% positive predictive value. In rare cases, the diagnosis may be unclear, and PCR of aqueous or vitreous humor specimens for CMV and other pathogens—especially herpes simplex virus, varicella zoster virus, and *Toxoplasma gondii*—can be useful for establishing the diagnosis. Detection of CMV DNA in CSF or vitreous or aqueous humor specimens is highly suggestive that CMV is the cause of ocular disease. In one study, CMV DNA was detected in 82% of vitreous specimens collected at diagnosis of CMV retinitis, in 77% of relapsed retinitis, and in 23% of quiescent retinitis.[10] Therefore, failure to detect CMV DNA in vitreous specimens does not rule out the presence of CMV retinitis. A response to empiric anti-CMV therapy also can be an important diagnostic indicator.

CMV colitis usually is diagnosed based on demonstration of mucosal ulcerations on endoscopic examination, combined with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions on hematoxylin and eosin stains.[2,11] Similarly, CMV esophagitis is diagnosed by presence of ulcers of the distal esophagus together with biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.[2] The number of inclusion bodies in specimens varies from many inclusion bodies to rare or isolated inclusion bodies. Immunohistochemistry also may be used to detect CMV in tissue. Culturing CMV, or detection of CMV DNA by PCR, from a biopsy or cells brushed from the colon or the esophagus is insufficient to establish the diagnosis of CMV colitis or esophagitis in the absence of histopathologic changes, because a substantial number of patients with low CD4 cell counts may shed CMV and have positive cultures in the absence of clinical disease.[12]

The diagnosis of CMV pneumonitis requires consistent clinical and radiological findings (i.e.,

diffuse pulmonary interstitial infiltrates, fever, and cough or dyspnea), identification of multiple CMV inclusion bodies in lung tissue or cytology, and the absence of any other pathogens that are more commonly associated with pneumonitis.[13] Detection of CMV in the lungs in the absence of these criteria typically represents shedding, rather than clinical disease.

CMV neurologic disease is diagnosed on the basis of a compatible clinical syndrome and the presence of CMV in CSF or brain tissue, most often evaluated with PCR.[3,14,15] Blood tests to detect CMV by antigen detection, culture, or PCR are not recommended for diagnosis of CMV end-organ disease because of their poor positive predictive value in people with advanced AIDS.[16] CMV viremia can be detected by PCR, antigen assays, or culture and is often present in endorgan disease. A negative serum or plasma PCR assay does not rule out CMV end-organ disease. CMV viremia may be present in the absence of end-organ disease in people with HIV with low CD4 cell counts.[9,12–15,17] Monitoring for CMV viremia is not recommended.

The presence of serum antibodies to CMV, in and of itself, does not establish the presence of CMV disease, because a large proportion of the general population has been exposed to CMV and is seropositive. However, a negative immunoglobulin G (IgG) antibody level indicates that CMV is unlikely to be the cause of the disease process.

Preventing Exposure

Although CMV infection is common in the general population, geographic, socioeconomic, and racial and ethnic differences exist in CMV prevalence.[10] In the National Health and Nutrition Examination Survey (NHANES) 1999–2004, CMV seropositivity was associated with older age, female sex, foreign birthplace, and markers of socioeconomic status, such as low household income and education and high household crowding. Some people with HIV may belong to groups with relatively low seroprevalence rates for CMV and, therefore, cannot be presumed to be seropositive. Adolescents and adults with HIV should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms used during sexual contact reduce the risk of exposure to CMV, as well as other sexually transmitted pathogens **(AII)**.

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4 count >100 cells/mm³ **(BI)**. A randomized, placebo-controlled trial addressed whether valganciclovir (the current standard oral agent for treatment of CMV disease) in addition to ART might reduce CMV end-organ disease in AIDS patients at high risk (CD4 count <100 cells/mm³ and CMV viremia detected by plasma CMV DNA PCR assay).[18] This study failed to show a benefit for such preventive therapy; therefore, valganciclovir primary prophylaxis **is not recommended** to prevent CMV end-organ disease in people with HIV, even among patients who have CMV viremia **(AI)**.

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy. Patients who have a low CD4 cell count (<100 cells/mm³) and are not on ART should be made aware of the implications of increased floaters in the eye and be advised to assess their visual acuity regularly using simple techniques, such as reading newsprint. Development of floaters or changes in visual acuity should prompt an urgent referral to ophthalmology **(AIII)**. In the premodern ART era, some specialists recommended ophthalmologic examinations every 3 to 4 months for patients with CD4+ cells <50 cells/mm³, because up to one-half of early CMV retinitis was asymptomatic **(CIII).** However, with the decline in CMV incidence in the modern ART era, the value of this recommendation is unknown. Some clinicians do recommend a baseline ophthalmologic exam for people with HIV with CD4 <100 cells/mm³ **(CIII)**.

Treating Disease

The therapeutic approach to CMV retinitis should be individualized based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and possibly the location of lesions (**AIII**). CMV retinitis should ideally be treated with the active participation of an ophthalmologist who is familiar with the diagnosis and management of this retinal disease **(AIII)**.

Oral valganciclovir **(AI)**, intravenous (IV) ganciclovir **(AI)**, or IV ganciclovir induction followed by oral valganciclovir maintenance **(AI)** are first-line therapies for treating CMV retinitis. Although IV foscarnet **(BI)**, and IV cidofovir **(CI)** are also effective treatments for CMV retinitis, substantial toxicities, including nephrotoxicity, make these less-preferred options.[8,19–26] Systemic therapy has been documented to reduce CMV involvement of the contralateral eye,[19] to reduce CMV visceral disease, and to improve survival.[20,27] Given the evident benefits of systemic anti-CMV therapy, treatment regimens for CMV retinitis should include a systemic component. Few trials have compared regimen efficacy during the past 15 years. None of the listed regimens has been proven in a clinical trial to have superior efficacy related to protecting vision. Therefore, clinical judgment must be used when choosing a regimen.[21–25]

When systemic therapy is indicated, most clinicians will prescribe IV ganciclovir **(AI)** or oral valganciclovir **(AI)** for an induction period lasting a minimum of 14 to 21 days, with the duration determined by clinical response based on retinal examination. Many prefer the IV formulation when retinitis is more central and sight-threatening or when adequate gastrointestinal (GI) absorption is a concern. In such cases, the patient's transition to oral valganciclovir can be considered when there is evidence of clinical response. In cases where toxicity of ganciclovir and valganciclovir (i.e., severe cytopenias) is a concern and there is not renal insufficiency, or when ganciclovir-resistant CMV is a concern, IV foscarnet may be used **(BI)**. IV cidofovir is rarely used, unless there is the need to avoid both ganciclovir and foscarnet **(CI)**. Cidofovir administration is complicated by the need to co-administer IV fluid hydration and probenecid to counter the nephrotoxicity of the drug. In addition, IV cidofovir is associated with increased risk of immune recovery uveitis, hypotony, and neutropenia.[28]

In the presence of immediately sight-threatening lesions (those within 1,500 microns of the fovea or optic disc) at presentation **(AIII)**, some clinicians will supplement systemic therapy with intravitreous injections of ganciclovir or foscarnet, at least initially, to provide immediate, high intraocular levels of the drug and presumably faster control of the retinitis **(AIII).** Injections are continued on a weekly basis until lesion inactivity is achieved, at which time systemic treatment alone is considered to be adequate for maintenance therapy. The recommendation to supplement systemic therapy with intravitreous injections is based on pharmacokinetic considerations, but the clinical benefit of such supplementation has not been confirmed in clinical trials. Although intravitreous injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are being achieved over time with systemically delivered medications,[19] such injections can be complicated by bacterial or fungal infections, hemorrhage, or retinal detachment. Repeated intravitreous injections of ganciclovir or of foscarnet alone have appeared to be effective for maintenance therapy of CMV retinitis in uncontrolled case series,[29] but this strategy should be reserved for those individuals who cannot be treated systemically. Intravitreous cidofovir is associated with hypotony and uveitis—and a substantially increased risk of immune recovery uveitis—and should be avoided (**AIII**).[30]

For patients without sight-threatening lesions, oral valganciclovir alone often is adequate **(AI)**. The ganciclovir implant, a surgically implanted reservoir of ganciclovir that lasts for approximately 6 months, is no longer manufactured.

Treatment with systemic anti-CMV therapy, such as oral valganciclovir for the first 3 to 6 months until ART has induced immune recovery, is beneficial (**AII**). Ocular complications, such as immune recovery uveitis (IRU) and retinal detachment, are related to lesion size, so minimizing lesion size with anti-CMV therapy until immune recovery is sufficient to control the retinitis is logical. Furthermore, evidence from both the pre-ART and ART eras demonstrate that specific anti-CMV therapy decreases mortality among immune-compromised patients with CMV retinitis.[12,20,26,31]

For patients who have colitis or esophagitis, many HIV specialists recommend anti-CMV therapy for 21 to 42 days **(CII)** or until signs and symptoms have resolved. IV ganciclovir generally is the therapy of choice and can be switched to oral valganciclovir once the patient can tolerate and absorb oral medications **(BI)**. Foscarnet can be used as an alternative if ganciclovir-related toxicity is treatment-limiting or in cases of ganciclovir-resistant virus **(BIII)**. Oral valganciclovir can be used in patients with mild disease **(BIII)**.

Experience treating well-documented CMV pneumonia in patients with HIV infection is limited and anecdotal. Treatment with IV ganciclovir or, alternatively, with foscarnet, is logical **(CIII)**. The optimal duration of therapy and the role of oral valganciclovir have not been established.

Therapy for well-documented neurologic disease also has not been extensively studied. Given the poor outcomes in many patients with CMV-related neurologic disease, some experts would initiate therapy with both IV ganciclovir and IV foscarnet, despite the substantial toxicities associated with such an approach **(CIII)**. The optimal duration of therapy and the role of oral valganciclovir have not been established.

Special Considerations with Regard to Starting Antiretroviral Therapy

Immune reconstitution inflammatory syndrome (IRIS) from CMV may occur in patients who have active retinitis and those who have had CMV retinitis in the recent or distant past. One study demonstrated a substantial increase in immune reconstitution uveitis (IRU) in association with immediate, as opposed to deferred initiation of ART (71% vs. 31%).[32] However, in the current era, the rate of clinically significant IRU following initiation of ART appears to be low (approximately 0.02 per person-year). Delaying ART until retinitis is controlled may reduce the likelihood or severity of IRU; however, this strategy must be weighed against the potential for a worsened immunocompromised state and the occurrence of other OIs. Several trials have demonstrated benefits of early versus delayed ART, including reduced risk of mortality, reduced AIDS progression, and shorter time to viral suppression.[33–36] Only one study has evaluated the benefits of early ART during treatment of an active OI, and it included few participants with CMV disease.[34]

As CMV replication usually declines within 1 to 2 weeks after anti-CMV therapy is initiated, most experts would initiate ART no later than 1 to 2 weeks after starting anti-CMV therapy for retinitis, esophagitis, colitis, or other end-organ diseases caused by CMV **(CIII)**. IRIS is a particular concern with any neurologic disease, including CMV encephalitis, ventriculitis, and radiculitis. In these cases, however, most experts would not defer initiation of ART for more than 2 weeks, although clinical judgment based on individual cases is needed **(CIII).**

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Indirect ophthalmoscopy of both eyes through dilated pupils should be performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment **(CIII)**. The purpose of such examinations is to evaluate efficacy of treatment, identify second eye involvement in cases of unilateral disease, and detect IRU or such complications as retinal detachment. Monthly fundus photographs, using a standardized technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early lesion reactivation. For patients who have experienced immune recovery (CD4+ count >100 cells/mm^3 for ≥3 months), the frequency of ophthalmologic follow-up can be decreased to every 3 months, but clinicians should be aware that lesion reactivation and retinal complications still occasionally occur in patients with immune reconstitution.

Adverse effects of ganciclovir/valganciclovir include anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Ganciclovir-related neutropenia often can be reversed with granulocyte colony stimulating factor (G-CSF).[33,34] In patients receiving ganciclovir or valganciclovir,

complete blood counts and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy **(AIII)**. Adverse effects of foscarnet include nephrotoxicity and electrolyte abnormalities; seizures that occur characteristically in the context of renal insufficiency; and anemia. Genital ulcers also can occur during foscarnet administration in those who are incontinent to urine due to the toxic effects of excreted drug on exposed skin. Foscarnet often is given in the inpatient setting because of the intensity of monitoring and need for hydration. For patients receiving foscarnet in the outpatient setting, serum electrolytes (including potassium, magnesium, calcium, and phosphorus) and renal function should be measured at least twice weekly during induction and at least weekly during maintenance therapy. Complete blood counts should be monitored weekly **(AIII)**.

Adverse effects of cidofovir include dose-related nephrotoxicity, neutropenia, uveitis, and hypotony (low intraocular pressure). The risk of severe renal injury from IV cidofovir can be reduced by prehydration and oral probenecid before cidofovir administration. In patients receiving IV cidofovir, analysis of blood urea nitrogen and creatinine levels and urinalysis should be performed before each infusion. Drug administration is contraindicated if renal dysfunction or substantial proteinuria is detected. Particular attention is needed for patients receiving other potentially nephrotoxic medications, including tenofovir disoproxil fumarate. Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony, even when CMV disease does not include retinitis.

As noted previously, patients with CMV retinitis must have careful ophthalmologic monitoring to detect and manage the wide range of complications related to CMV, the drugs used to treat CMV, and IRIS. IRU, an ocular form of IRIS presumed to be an adverse immunologic reaction to CMV, is characterized by inflammation in the anterior chamber or vitreous body in the setting of immune recovery after initiation of ART. IRU usually is observed in patients with a substantial rise in CD4 cell count in the first 4 to 12 weeks after initiation of ART.[28,35–38] The estimated incidence of IRU is 0.02/person-year after immune recovery.[39] Ocular complications of IRU include macular edema and development of epiretinal membranes, which can cause loss of vision. Although the inflammatory reactions seen at the onset of IRU can be transient as immune reconstitution occurs, the complications may persist, permanently compromising vision.

Treatment of IRU usually consists of some type of corticosteroid therapy. The benefit of anti-CMV therapy is unclear.[35,40] Many experts would use both corticosteroids and anti-CMV therapy **(CIII)**. Data are insufficient on which to base a recommendation regarding the preferred route of corticosteroid administration; periocular, intravitreous, and oral administration all have been reported to be potentially successful. When oral corticosteroids are used, a short course rather than chronic therapy usually is recommended **(BIII)**.[41] IRU can occur months or years after successful treatment of CMV retinitis in patients with a history of CMV retinitis who subsequently start taking ART or have such therapy optimized.

People with advanced HIV remain at risk for development of CMV retinitis prior to immune reconstitution, even after initiation of ART.[42,43] Development of CMV retinitis in the setting of recent ART initiation should be treated with systemic anti-CMV therapy, similar to any patient with CMV retinitis, and the same ART regimen should be continued **(AI)**. Corticosteroids are not recommended **(AIII)**. In addition, in the absence of uveitis, corticosteroids should not be used in patients undergoing treatment for CMV retinitis who have worsening of retinitis upon ART initiation. In this situation, anti-CMV therapy and ART regimens should be continued **(AIII)**.

Managing Treatment Failure
Failure of therapy for CMV retinitis or reactivation of lesions is most likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART.[44] Treatment failure

also may be a result of inadequate anti-CMV drug levels in the eye, CMV drug resistance, or nonadherence. Many experts believe that early progression of disease (enlargement of lesions or new lesions) is most often caused by the limited intraocular penetration of systemically administered drugs.[40,45,46]

When reactivation of lesions occurs in patients receiving maintenance therapy, retinitis usually can be controlled with re-induction of the same drug used for maintenance followed by re-institution of maintenance therapy (**BIII**).[47] Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy and for patients with continued progression or multiple reactivations of retinitis (**CIII**).[47] This drug combination, however, is associated with substantial toxicity.

Drug resistance can occur in patients receiving long-term anti-CMV therapy.[48–51] Drug resistance rates of approximately 25% per person-year were reported in the pre-ART era[48,52,53] for ganciclovir, foscarnet, and cidofovir.[48,49] In the ART era, the rate of resistance appears to be lower (approximately 5% per person-year).[54] Low-level resistance to ganciclovir occurs through mutations in the CMV UL97 (phosphotransferase) gene, and high-level resistance to ganciclovir typically occurs because of mutations in both the CMV UL97 and UL54 (DNA polymerase) genes.[50,55–59] Resistance to foscarnet or cidofovir occurs because of mutations in the CMV UL54 gene. High-level resistance to ganciclovir often is associated with cross-resistance to cidofovir[57] and occasionally to foscarnet.[58] Although early CMV disease progression typically is not a result of drug resistance, late CMV reactivation may be. By themselves, peripheral blood CMV viral load measurements have poor positive predictive value for treatment failure.

Ganciclovir resistance in patients who fail therapy can be detected by CMV DNA PCR of blood specimens followed by detection of UL97 mutations by DNA sequencing or by a point mutation assay[60–62] Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in less than 48 hours and correlates well with conventional drug susceptibility testing and clinical outcomes.[62] Circulating CMV in blood and vitreous fluid have identical UL97 sequences in more than 90% of cases;[63] therefore, evaluating the blood for resistance is reasonable, and detection of resistance in the blood or urine correlates with clinical behavior of the retinitis in most cases.[64] Viral culture and susceptibility testing and viral DNA sequencing often are not available in clinical laboratories because they are too time consuming or costly. UL97 mutants usually respond to foscarnet, as do some UL54 mutants.[65] Many clinicians will treat ganciclovir-resistant CMV with a series of intravitreous injections of foscarnet and/or IV foscarnet or cidofovir (**CIII**).

Preventing Recurrence

When to Start Maintenance Therapy

After induction therapy for CMV retinitis, chronic maintenance therapy should be continued,[9,14,19,22,66] until immune reconstitution occurs as a result of ART (**AI**). Maintenance therapy is started after induction has achieved control of retinitis, as evidenced by resolved or markedly reduced retinal lesion opacity, indicating virus inactivity. Although several regimens are effective for chronic suppression—including parenteral ganciclovir, parenteral foscarnet, and parenteral cidofovir—oral valganciclovir may be the easiest and least toxic to administer to an outpatient population, provided that GI absorption is adequate. Systemic therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred.

The choice of regimen (i.e., which drug[s] and whether given intravitreously, orally, or intravenously) should be made in consultation with an ophthalmologist. Considerations should include the anatomic location of the retinal lesion; vision in the contralateral eye; and a patient's immunologic and virologic status, comorbidities, concomitant medications, and response to ART.

After resolution of the acute CMV syndrome and initiation of effective ART, chronic mainte-

nance therapy is not routinely recommended for CMV GI disease, pneumonitis, and central nervous system disease unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially (**BII**).

When to Stop Maintenance Therapy

Maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose lesions have been treated for at least 3 to 6 months and are inactive and who have had sustained (i.e., 3–6 months) increases in CD4 cell counts to >100 cells/mm^3 in response to ART (**AII**).[4,67–73] Such decisions should be made in consultation with an ophthalmologist. A 3% reactivation rate is reported in patients whose anti-CMV therapy has been discontinued for immune recovery, and no level of CD4 cell count is absolutely safe (reactivations have been reported at CD4 cell counts of 1,250 cells/mm^3). Therefore, in all patients for whom anti-CMV maintenance therapy has been discontinued, ophthalmologic monitoring for early detection of CMV relapse and for IRU should be performed at least every 3 months and periodically after immune reconstitution (**AIII**). Monitoring CMV viral load in blood has poor positive predictive value for relapse of retinitis and, therefore, is not recommended (**AII**).[16]

Reactivation of CMV retinitis occurs frequently in patients whose CD4 cell counts have decreased to <50 cells/mm^3 and whose anti-CMV maintenance therapies have been discontinued.[74] Therefore, reinstitution of maintenance therapy should occur when the CD4 cell count has decreased to <100 cells/mm^3 (**AIII**).

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for nonpregnant women. Indications for treatment of CMV infection during pregnancy are the same as for nonpregnant people with HIV (**AIII**). For retinal disease, use of intravitreous injections for local therapy should be considered in the first trimester, if possible, to limit fetal exposure to systemically administered antiviral drugs (**BIII**). Systemic antiviral therapy should then be started after the first trimester. For life-threatening indications, treatment with systemic antiviral therapy during the first trimester may be necessary.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits.[75–77] However, safe use in all trimesters of human pregnancy after organ transplantation and in other patient populations has been reported.[75–79]

Foscarnet is associated with an increase in skeletal anomalies or variants in rats and rabbits. No experience with use early in human pregnancy has been reported. A single case report of use in the third trimester described normal infant outcome.[80] Because toxicity of foscarnet is primarily renal, weekly monitoring of amniotic fluid volumes by ultrasound is recommended after 20 weeks of gestation to detect oligohydramnios if foscarnet is used.

Cidofovir is embryotoxic and teratogenic (i.e., meningomyelocele and skeletal abnormalities) among rats and rabbits. No experience with use of cidofovir in human pregnancy has been reported; use in pregnancy is not recommended (**AIII**).

On the basis of limited data, toxicity reports, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy (**BIII**). The fetus should be monitored by fetal-movement counting in the third trimester and by periodic ultrasound monitoring after 20 weeks of gestation to look for evidence of hydrops fetalis indicating substantial anemia. No data exist to support use of pooled or CMV-specific intravenous immunoglobulin in this clinical situation.

Primary infection, reactivation, and reinfection with a different strain of CMV during pregnancy (non-primary infection)[81] all can lead to *in utero* transmission and congenital CMV. Maternal ART in pregnancy has been associated with decreased rates of perinatal/early postnatal CMV and decreased

CMV-related clinical symptoms among infants exposed to or infected with HIV.[82] Recent studies indicate the prevalence of congenital CMV among infants in the United States who are exposed to HIV is 1.2% to 1.3%.[83] Risk factors for congenital CMV include mothers with CD4+ <200 cells/mm^3, mothers with urinary CMV shedding,[84] and HIV transmission to infants. Maternal CMV and infant congenital CMV also have been associated with increased risk of HIV perinatal transmission in pregnant women with HIV who have not received antenatal ART.[85]

   In women diagnosed with primary CMV infection in pregnancy, the fetus should be monitored by periodic ultrasound after 20 weeks gestation **(CIII)**. In studies in HIV-uninfected populations, about 5% to 25% of newborns infected with CMV had ultrasound evidence of congenital infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel).[86] Any ultrasound findings suspicious for congenital CMV infection should prompt consideration of invasive testing (i.e., amniocentesis) for definitive diagnosis. Referral to a maternal–fetal medicine specialist for evaluation, counseling, and potential further testing is recommended. Potential noninvasive biomarkers for predicting congenital CMV infection are under study.[87]

   If fetal CMV infection is confirmed, no standard therapy exists for *in utero* treatment. Available clinical studies support the possible effectiveness and safety of CMV hyperimmune globulin in pregnancy for prevention or treatment of congenital CMV.[88,89] A nonrandomized trial of CMV hyperimmune globulin in women not infected with HIV with primary CMV infection in pregnancy found decreased incidence of having a symptomatic newborn at birth[90] and regression of fetal cerebral abnormalities;[91] however, a well-designed, prospective, randomized, placebo-controlled study with relatively large sample size subsequently found no benefit of CMV hyperimmune globulin in pregnant women.[88,92,93] A second randomized clinical trial that planned to enroll 800 patients with primary CMV infection at <24 weeks gestation was stopped for futility after enrollment of 399 participants when a planned interim analysis suggested that complete enrollment would not provide a significant outcome.[93]

   Routine screening for CMV infection in pregnancy is not recommended in the absence of effective *in utero* therapy. Treatment of asymptomatic maternal CMV infection during pregnancy solely to prevent infant infection is not indicated **(AIII)**.

Recommendations for Treating Cytomegalovirus Infections

Preventing CMV Disease

- CMV end-organ disease is best prevented by using ART to maintain CD4+ count >100 cells/mm³.

Managing CMV Retinitis

- The choice of therapy for CMV retinitis should be individualized, based on tolerance of systemic medications; prior exposure to anti-CMV drugs; and on the location of lesions **(AIII)**.
- Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reducing CMV visceral disease, and improving survival, treatment should include systemic therapy whenever feasible.

Initial Therapy Followed by Chronic Maintenance Therapy—For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea)

Preferred Therapy

- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily **(AI)**, *or*
- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily **(AI)**, *or*
- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily **(AI)**; *or* with or without
- Intravitreous injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) repeat weekly until lesion inactivity is achieved. This is to provide higher intraocular levels of drug and faster control of the infection until steady-state intraocular ganciclovir concentrations are achieved. **(AIII)**
  - **Note:** IV ganciclovir can be switched to oral valganciclovir if the patient is clinically improving and there are no concerns about gastrointestinal absorption.

Alternative Therapy

- Intravitreous injections as listed above **(AIII)**; plus one of the following systemic therapies:
  - Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h **(BI)**, *or*
  - Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) **(CI)**. Cidofovir is contraindicated in patients with a serum creatinine >1.5 mg/dL, a calculated creatinine clearance ≤55 mL/min or a urine protein ≥100 mg/dL (equivalent to ≥2+ proteinuria). Given the nephrotoxic potential of cidofovir, cautious use of cidofovir with tenofovir is advised
    - **Note:** This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid.

For Peripheral Lesions

- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily **(AI)** for the first 3–6 months until ART-induced immune recovery **(AII)**.

IRU

- Minimizing lesion size by treating all CMV retinitis lesions until there is immune recovery may reduce the incidence of IRU **(BII)**.
- IRU might develop in the setting of immune reconstitution.

Treatment of IRU

- Periocular or intravitreal corticosteroid or a short course of systemic steroid **(BIII)**.

Stopping Chronic Maintenance Therapy for CMV Retinitis

- CMV treatment for at least 3–6 months, <u>and</u> lesions are inactive, <u>and</u> with CD4+ count >100 cells/mm³ for 3–6 months in response to ART **(AII)**.
- Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of CD4 cell count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring.
- Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution **(AIII)**.

Reinstituting Chronic Maintenance for CMV Retinitis

- CD4 count <100 cells/mm³ **(AIII)**.

Managing CMV Esophagitis or Colitis
•   Doses are the same as for CMV retinitis. *Preferred Therapy* •   Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy **(BI)**. *Alternative Therapy* •   Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h **(BIII)**—for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance; *or* •   Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption **(BIII)**; *or* *Duration of Anti-CMV Therapy* •   21–42 days or until signs and symptoms have resolved **(CII)**. **Note:** Maintenance therapy is usually not necessary, but should be considered after relapses **(BII)**.
Managing <u>Well-Documented</u> CMV Pneumonitis
•   Doses are the same as for CMV retinitis. •   Treatment experience for CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable **(CIII)**. •   The role of oral valganciclovir has not been established. •   The optimal duration of therapy has not been established.
Managing CMV Neurological Disease
•   Doses are the same as for CMV retinitis. •   <u>Treatment should be initiated promptly</u>. •   Combination of ganciclovir IV plus foscarnet IV to stabilize disease and maximize response **(CIII)**. •   Optimal duration of therapy has not been established. •   The role of oral valganciclovir has not been established. •   Optimize ART to achieve viral suppression and immune reconstitution **(BIII)**.

Key to Acronyms: ART = antiretroviral therapy; BID = twice a day; CMV = cytomegalovirus; IRU = immune recovery uveitis; PO = orally; IV = intravenously; q(n)h = every "n" hours

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Hepatitis B Virus Infection

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Epidemiology

After acquiring hepatitis B virus (HBV) infection, many adults spontaneously recover and develop protective hepatitis B surface antibodies (anti-HBs). However, some progress to chronic hepatitis B, which is a leading cause of chronic liver disease worldwide.[1-6] Globally and in North America, approximately 8% of people with HIV have evidence of chronic HBV infection, but this varies by region of the world.[7]

Transmission routes vary geographically, with perinatal and early-childhood exposures responsible for most HBV transmission in higher-prevalence regions.[8] In low-prevalence regions—such as Europe and North America—a large proportion of transmission is through sexual contact and injection drug use, but perinatal transmission also occurs.[9] Although the general modes of transmission are similar to those of HIV, HBV is transmitted more efficiently than HIV.[4,6] People with HIV are at increased risk for developing chronic HBV infection.[10] Ten genotypes of HBV (A–J) have been identified, and their geographic distributions differ,[11] with genotype A being most common in North America and Western Europe, genotypes B and C in Asia, and genotypes A, D, and E in sub-Saharan Africa in people with HBV infection.[12,13]

Approximately 5% of people with chronic HBV infection are coinfected with hepatitis D virus (HDV), which requires HBV for its propagation since it uses the hepatitis B surface antigen as its envelope.[14] Thus, prevalence of HDV mirrors that of chronic HBV infection.

Clinical Manifestations

HBV has an average incubation period of 90 days (range 60–150 days) from exposure to onset of symptoms.[15] Acute HBV infection is asymptomatic in approximately 70% and <1% develop fulminant hepatic failure.[1,16] When symptoms manifest, they may include right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias with or without jaundice. Most people with chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue. Between 15% and 40% of people with chronic HBV infection will eventually develop cirrhosis, hepatocellular carcinoma (HCC), or liver failure, and up to 25% of people will die prematurely from complications of chronic HBV infection.[17]

Diagnosis

Centers for Disease Control and Prevention (CDC) recommends testing all people over the age of 18, including those with HIV, for chronic HBV infection.[18] Initial testing should include a triple screening panel of serologic testing for HBV surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and anti-HBs.[18] In acute infection, HBsAg can be detected 4 weeks (range 1–9 weeks) after exposure, and anti-HBc immunoglobulin M (IgM) is usually detectable at the onset of symptoms. See CDC's Clinical Testing and Diagnosis for Hepatitis B for information on how to interpret laboratory results.

Chronic HBV infection is defined as persistent HBsAg detected on two occasions at least 6 months apart.[1] People with chronic HBV infection should be tested further for HBV e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. "Active" disease, which can be HBeAg negative or HBeAg positive, can be distinguished from inactive disease by the presence of both serum HBV DNA and persistent or fluctuating alanine transaminase (ALT) elevations, defined as ≥2 times the upper limit of normal (≥70 U/L for males and ≥50 U/L for females).[1] Because people with chronic HBV infection are at risk for coinfection with HDV, anti-HDV should be checked once chronic HBV infection is diagnosed. If positive, then HDV RNA should be obtained to look for chronic infection.

In a low-prevalence country—such as the United States—isolated anti-HBc also may represent a false-positive result. However, the presence of an isolated positive anti-HBc test result can signify infection with HBV in the past with subsequent loss of anti-HBs. Isolated anti-HBc occurs in 7% to 19% of people with HIV.[19-22] Frequency of HBV viremia among people with HIV and isolated anti-HBc typically ranges from 1% to 10%.[19,20,23,24] Because most people with HIV with isolated anti-HBc are HBV DNA negative,[25] routinely checking HBV DNA is not recommended. The clinical significance of isolated anti-HBc is unknown,[19,22,26-28] but in people with HIV, it may indicate chronic or, more likely, resolved HBV infection.[29] People with HIV—particularly those with underlying hepatitis C virus (HCV) coinfection—have a higher frequency of isolated anti-HBc.[21,25,30,31]

People whose past infection has resolved are HBsAg negative with positive anti-HBs and anti-HBc.[1,32]

Diagnosing HBV Disease Progression and the Role of Assessing Liver Fibrosis

Compared with people with HBV mono-infection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[33] People with HIV/HBV are also more likely to have detectable HBeAg,[33,34] lower rates of seroconversion to anti-HBe, and increased risk of HCC and liver-related mortality and morbidity.[35-37]

Chronic HBV infection is a dynamic disease with a number of phases (see the [American Association for the Study of Liver Diseases' 2018 Hepatitis B Guidance](#)). In HIV/HBV coinfection, monitoring and treatment are focused on the simultaneous and immediate treatment of both viruses regardless of HBV phase.

People with HIV and chronic HBV should be linked to care and have a complete history and physical examination for signs of cirrhosis or HCC. HBV serologic and quantitative nucleic acid testing (HBeAg/anti-HBe and HBV DNA) and other laboratory testing—complete blood count, ALT, aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase, international normalized ratio (INR), hepatitis A virus (HAV) immunoglobulin G (IgG) (to determine the need for vaccination), HCV IgG (if positive, HCV viral load), antibodies to hepatitis D virus IgG (if positive, HDV RNA), abdominal ultrasound, and liver fibrosis assessments (transient elastography or serum markers e.g. Fibrosure)—should be performed at the initial visit.[1] The decision to perform a liver biopsy should be individualized, but the procedure is rarely necessary.[1] People with chronic HBV infection are at increased risk of HCC; therefore, HCC surveillance every 6 months (ultrasound with or without alfa fetoprotein) is required for people who have cirrhosis and for people in the following groups who are at increased risk of disease progression: Asian males older than age 40, Asian females older than age 50, and males older than age 20 who are from sub-Saharan Africa.[1] People with HIV/HBV coinfection are at increased risk of HCC,[38,39] and some experts recommend ongoing

semi-annual HCC surveillance for all people aged 40 years and older with HIV/HBV coinfection **(BIII).**

Preventing Disease

See the [Hepatitis B Virus row of the Recommended Adult Immunization Schedule by Medical Condition and Other Indications table](#) in the [Immunizations for Preventable Diseases in Adults and Adolescents With HIV](#) chapter for a summary of HBV vaccination recommendations. The evidence summary in this section will be moved to the [Immunizations chapter](#) in the next update.

All family members and sexual contacts of people with chronic HBV infection should be tested, and all susceptible household and sexual contacts should receive hepatitis B (HepB) vaccine regardless of whether they have HIV **(AII).** All people with HIV who are not immune to HBV infection (anti-HBc and anti-HBs negative) and do not have chronic HBV, as well as those who have failed a prior HBV vaccine series, should receive HepB vaccination with one of the available vaccines **(AII).**

Available adult single-antigen HepB vaccines in the United States that have been studied in people with HIV include two recombinant HBsAg vaccines (Engerix-B and Recombivax HB) and a recombinant HBsAg vaccine conjugated to a cytosine phosphoguanine oligonucleotide adjuvant (HepBCpG), which is a toll-like receptor 9 agonist (Heplisav-B).

The preferred vaccine in previously unvaccinated patients is Heplisav-B given at 0 and 4 weeks **(AII).** A single-arm study in 68 people with HIV, who were naive to HepB vaccine, and received Heplisav-B at 0, 4, and 24 weeks demonstrated a seropositivity rate (anti-HBs >10 mIU/mL) at 4 weeks and 20 weeks after the second dose of 87% and 98.5%, respectively.[40] The seropositivity rate 4 weeks after the third dose was 100%.

A two-dose Heplisav-B is appropriate only when both doses are Heplisav-B. In other situations, three total doses of vaccine should be given **(AI).** If Heplisav-B is not available, then vaccinate either with double-dose vaccine Engerix-B or double-dose Recombivax HB as the primary three-dose series **(AII),** or combined HepA and HepB (i.e., Twinrix) as a three-dose series **(AII).** A meta-analysis of 10 studies of people with HIV demonstrated that compared to a single dose, a double dose of Engerix-B or Recombivax HB had better response rates at 4 to 6 weeks (odds ratio [OR] 1.76; 95% confidence interval [CI], 1.36–2.29) and at >12 months (OR 2.28; 95% CI, 1.73–3.01) after vaccine completion.[41] A double dose of Engerix-B is 40 mcg (two injections of the 20-mcg dose). A double dose of Recombivax HB is 20 mcg (two injections of the 10-mcg dose).

The magnitude and duration of immunogenicity to HepB vaccination with the two recombinant vaccines (Engerix-B, Recombivax HB) in adults with HIV are significantly lower than in healthy adults who are HIV seronegative.[42-44] Factors associated with poor response to these two recombinant vaccines include low CD4 T lymphocyte (CD4) cell counts,[42,45-50] presence of detectable HIV RNA,[46,50,51] coinfection with HCV, occult HBV infection, and the general health status of the host.[20,25,52-56] Although vaccine response to the two recombinant vaccines is better when CD4 counts are >350 cells/mm^3, vaccination should not be deferred until CD4 counts increase to >350 cells/mm^3 in those at high risk for HBV infection because some people with HIV with CD4 counts ≤350 cells/mm^3 do respond to vaccination **(AII).**

Response to HepB vaccination, defined as anti-HBs ≥10 mIU/mL, should be documented 4 weeks after the last dose of vaccine **(AII).** In an observational study of 409 people with HIV who received

the HepB vaccine, those with anti-HBs ≥10 mIU/mL were less likely to develop breakthrough HBV infection compared to those who did not achieve that level.[57] In addition, among those with a breakthrough HBV infection, 0% of those with anti-HBs ≥10 mIU/mL developed chronic infection compared to 35% of those with anti-HBs <10 mIU/mL ($P = 0.02$).

In those who failed a prior vaccine series with Engerix-B or Recombivax HB, Heplisav-B at 0 and 4 weeks is recommended **(AI)**, and a third dose at 24 weeks can be considered since three doses results in higher anti-HBs titers **(BIII).** In a study of 561 people with HIV and prior nonresponse to Engerix-B or Recombivax HB, they were randomized to either Heplisav-B at 0 and 4 weeks, Heplisav-B at 0, 4, and 24 weeks, or Engerix-B at 0, 4, 24 weeks. Participants had CD4 counts >100 cells/mm^3 (median 635 cells/mm^3) and HIV RNA <1,000 copies/mL (94% <40 copies/mL). Four weeks after the last dose, the proportion with anti-HBs >10 mIU/mL (positive) was 93.1%, 99.4%, and 80.6% in two-dose Heplisav-B, three-dose Heplisav-B, and three-dose Engerix-B, respectively ($P < 0.05$). Of note, 96% of those who received the three-dose Heplisav-B had anti-HBs titers >100 IU/mL compared to 70% of those who received the two-dose Heplisav-B and 63% who received Engerix-B.[58] These data suggest that a third dose may be beneficial to provide more durable immunity but further follow-up is needed.

Because of waning immunity, some experts would check anti-HBs annually and give a booster dose if levels fall below 10 mIU/mL, particularly if a person has ongoing risk factors for acquiring HBV and is not receiving tenofovir **(CIII).**[59] Waning immunity is typically seen in people with low CD4 cell counts (<350 cells/mm^3) and may be a consequence of the height of the initial antibody response after immunization. In a study of people with HIV who had antibody titers assessed 4 weeks after completing the three-dose hepatitis B vaccine series, those who had a titer <100 mIU/mL were significantly more likely to have waning immunity over the next 5 years compared with individuals who had higher titers after vaccination.[60]

People with isolated anti-HBc should be vaccinated with one standard dose of HepB vaccine (one dose of Heplisav-B, or Engerix-B, or Recombivax HB), and anti-HBs titers should be checked 1 to 2 months after vaccination **(BII).** If the anti-HBs titer is ≥100 mIU/mL, no further vaccination is needed, but if the titer is <100 mIU/mL, a complete series of the same HepB vaccine should be completed and followed by anti-HBs testing **(BII).**[61] The cutoff of 100 mIU/mL is used in this situation because one study demonstrated that 100% of people with isolated anti-HBc who achieved a titer of 100 mIU/mL after a booster dose maintained an anti-HBs response for >18 months compared with only 23% of those who achieved a titer of 10 to 100 mIU/mL.[61] If anti-HBs quantitative titers are not available, then the complete series of HepB vaccine should be completed followed by qualitative anti-HBs testing **(BII).**

HBV-active ART (includes tenofovir with lamivudine [3TC] or emtricitabine [FTC]) decreases the risk for acute HBV infection, but it does not eliminate the risk, so taking ART alone is not a recommended strategy to prevent HBV infection. Therefore, HepB vaccine is recommended even if receiving an HBV-active ART regimen **(AIII).** In a study that evaluated HBV incidence in 591 males who have sex with men (MSM) with HIV, the HBV incidence rate for men not on HBV-active ART was 23.8 per 1,000 person-years (PYs) compared to 2.6 per 1,000 PYs for men on HBV-active ART with HIV RNA <400 copies/mL.[62] The protective effect against incident HBV was similar in those taking lamivudine- or tenofovir-containing ART regimens. In another report of 354 people with HIV and without prior HBV, the risk of new HBV infection was substantially reduced in those receiving HBV-active ART (hazard ratio 0.11, 95% CI 0.03–0.39); those receiving HBV-active ART who acquired HBV were taking lamivudine, and some acquired lamivudine-resistant virus.[63] The potential

benefit of a tenofovir- versus lamivudine-containing regimen in preventing HBV infection was examined in a study of 381 males with HIV and found HBV incidence rates to be 2.85, 1.36, and 0.14 cases per 100 PYs among those taking ART without hepatitis B virus antibody (anti-HBV) activity, lamivudine without tenofovir, and tenofovir, respectively.[64] In another study of 786 MSM on pre-exposure prophylaxis (PrEP), there were fewer incident HBV infections in persons who took tenofovir-based PrEP compared to those who did not take PrEP (3.8% vs. 0.8%, $P = 0.02$).[65]

Preventing Other Liver Diseases

Hepatitis A vaccination is recommended for all people with HIV, including pregnant people, who are HAV total (IgG plus IgM) antibody negative **(AIII).** Among people with HIV with CD4 counts <200 cells/mm^3, responses to the hepatitis A vaccine are reduced.[66,67] Antibody response should be assessed at least 1 month after vaccination is complete. If total HAV antibody (anti-HAV) immunoglobulin (IgG and IgM) is negative, people should be revaccinated when their CD4 count is >200 cells/mm^3 **(BIII).**

People with chronic HBV infection should be advised to avoid alcohol consumption **(AIII).**

Treating Hepatitis B Virus Infection

Recommendations for Treating Chronic Hepatitis B Virus Infection
Indication for Therapy
• All people with HIV/HBV coinfection (HBsAg positive), including pregnant people, regardless of CD4 count and HBV DNA level **(AII)**, should be treated with an ART regimen that includes drugs active against both HIV and HBV infections **(AII)**.
• Some experts recommend that people with isolated anti-HBc positivity receive an ART regimen that includes drugs active against HBV and HIV **(CIII)**. However, an ART regimen without HBV activity can be considered, provided HBV DNA is undetectable and the benefits outweigh the risks of potential HBV reactivation **(CIII)**. Please also see recommendations below in the Special Considerations When Initiating Nucleos(t)ide-Sparing Regimens section.
Preferred Therapy (CrCl ≥60 mL/min)
• The ART regimen should include two drugs active against HBV, preferably with—
○ TAF (10 or 25 mg)^a plus FTC 200 mg or TAF 25 mg plus 3TC 300 mg PO once daily **(AII)**, *or*
○ TDF 300 mg plus (FTC 200 mg or 3TC 300 mg) once daily **(AII)**
Preferred Therapy (CrCl 30–59 mL/min)
• The ART regimen should include two drugs active against HBV, preferably with—
○ TAF (10 or 25 mg)^a plus FTC 200 mg PO once daily **(AII)**
Preferred Therapy (CrCl <30 mL/min, Not Receiving HD)
• Renally dosed entecavir (in place of TDF/[FTC or 3TC] or TAF/FTC) **(AIII)**, with a fully suppressive ARV regimen), *or*
• ART with renally dose-adjusted TDF and (FTC or 3TC) **(AIII)** when recovery of renal function is unlikely.
• If CrCl ≥ 15 to 29 mL/min, then ART with TAF (10 or 25 mg) once daily plus renally dose-adjusted FTC or 3TC is an option **(AIII)**.
○ Some clinicians may choose to continue full-dose FTC or 3TC to allow for people with CrCl 15–29 mL/min to remain on fixed-dose TAF/FTC products.

Preferred Therapy (Receiving HD)

- ART with renally dose-adjusted TDF plus [FTC 200 mg or 3TC 300 mg once daily] **(AII)** *or*

- ART with TAF [10 or 25 mg]ᵃ plus FTC 200 mg PO once daily (given after HD on dialysis days) **(AII).** TAF and FTC do not require renal dose adjustment in people receiving HD; therefore, fixed-dose TAF/FTC products may be continued.

Note: See Table 6 for dosing recommendation for TDF, TAF, FTC, and 3TC for people with renal impairment.

Duration of Therapy/**Monitoring** During Therapy

- People on treatment for HBV and HIV should receive therapy indefinitely **(AIII)**.

- HBV DNA should be monitored at 6-month intervals **(AII)**.

- HBsAg should be monitored yearly **(AIII)**.

Special Considerations When Initiating Nucleos(t)ide-Sparing Regimens

- *In people without a history of chronic HBV infection*: Prior to initiating or switching to a nucleos(t)ide-sparing ARV regimen, HBsAg, anti-HBs, and anti-HBc should be checked to evaluate for unrecognized chronic HBV infection unless evaluated within the last 3 months **(AIII)**.

- *In people with chronic HBV infection (HBsAg positive):*

  o Anti-HBV therapy (TDF, TAF, or entecavir) must be given if there is a switch to a nucleos(t)ide-sparing ARV regimen **(AIII)**.

  o Switching to the one-pill regimen of DTG/3TC without additional anti-HBV therapy (TDF, TAF, or entecavir) should be avoided because 3TC is then the only active drug against HBV **(AIII)**.

  o Switching to DTG/RPV or long-acting CAB/RPV without addition of an anti-HBV drug (TAF, TDF, or entecavir) should be avoided **(AIII)**.

- *In people with isolated anti-HBc positivity*: Some experts recommend against switching to DTG/3TC or a nucleos(t)ide-sparing ARV regimen without additional anti-HBV therapy, but this could be considered if the benefits outweigh the risk of potential HBV reactivation **(CIII)**.

- *In people with anti-HBc and anti-HBs positivity*: Switch to a nucleos(t)ide-sparing ARV regimen without additional anti-HBV therapy is possible **(AIII)**.

Other Considerations

- Because people with HBV/HCV/HIV coinfection appear to have accelerated liver fibrosis progression, high risk of HCC, and increased mortality, treatment for both HBV and HCV infection should be initiated, if feasible **(AII)**.

- Because HBV reactivation can occur during treatment for HCV with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation **(AIII)**.

- When changing ART regimens, it is crucial to continue agents with anti-HBV activity due to risk of HBV reactivation with hepatic flare after stopping anti-HBV treatment **(AIII)**.

- If anti-HBV therapy must be discontinued, serum transaminase and HBV DNA levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter **(AIII)**.

- If a hepatic flare occurs after drug discontinuation, HBV therapy should be reinstituted because it can be potentially lifesaving **(AIII)**.

- If immunosuppressive therapy is given, HBV reactivation can occur.

  o People who are HBsAg positive should be administered treatment for HBV infection regardless of HBV DNA level **(AII)**.

- o For people who are HBsAg-negative/anti-HBc-positive, it is prudent to include TDF or TAF/FTC or 3TC as part of the ART regimen prior to immunosuppression to prevent reactivation **(BIII)**.

- o For people who are HBsAg-negative/anti-HBc positive, if TDF or TAF cannot be given, then they can either be monitored or be given prophylaxis with entecavir to prevent reactivation depending on the degree of immunosuppression and whether HBV DNA is detectable **(BIII)** (see Special Considerations During Immunosuppressive Therapy section below). If anti-CD20 is given, then treatment with entecavir is recommended regardless of HBV DNA **(AII)**.

- o Treatment should be continued for 6 months after immunosuppressive therapy is complete or for 12 months after anti-CD20 therapy is complete **(BIII)**.

Pregnancy Considerations
• TAF or TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone for pregnant people with chronic HBV infection **(AIII)**. • Infants born to people who are HBsAg positive should receive HBIG and HepB vaccine (first dose of three) within 12 hours of delivery **(AI)**. The second and third doses of vaccine should be administered at 1–2 months and 6 months of age, respectively **(AI)**.

[a] TAF 10 mg dose is in the fixed-dose combination tablets of elvitegravir/cobicistat/TAF/FTC and darunavir/cobicistat/TAF/FTC; when TAF is used with other antiretrovirals, the dose is 25 mg.

Key: 3TC = lamivudine; anti-HBc = HBV core antibody; anti-HBs = HBV surface antibody; anti-HBV = hepatitis A virus antibody; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CrCl = creatinine clearance; CAB = cabotegravir; DTG = dolutegravir; FTC = emtricitabine; HBsAg = HBV surface antigen; HBV = hepatitis B virus; HBIG = hepatitis B immune globulin G; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HD = hemodialysis; HepB = hepatitis B; NRTI = nucleoside reverse transcriptase inhibitor; PO = orally; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Preferred Regimens

The ultimate treatment goals in HIV/HBV coinfection are the same as for HBV mono-infection: to prevent disease progression and to reduce HBV-related morbidity and mortality. All people with HIV/HBV coinfection (HBsAg positive), including pregnant people, regardless of CD4 count and HBV DNA level **(AII),** should be treated with an antiretroviral (ART) regimen that includes drugs active against both HIV and HBV infections **(AII).**

The Adult and Adolescent Antiretroviral Guidelines recommend the fixed-dose coformulations of tenofovir disoproxil fumarate (TDF)/(FTC or 3TC), TAF/FTC, abacavir/3TC, or 3TC alone (with dolutegravir) as nucleoside reverse transcriptase inhibitor (NRTI) regimen backbones for ART-naive people regardless of CD4 count.[68] Because both components of the tenofovir combinations (tenofovir and either FTC or 3TC) have anti-HBV activity, they are also the treatment of choice for people with HIV/HBV coinfection **(AII)** regardless of CD4 count **(AI)** and HBV DNA level **(AII)** (see Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Antiretroviral Guidelines). TDF and TAF are both active against wild-type and 3TC-resistant HBV strains. Studies among people with HIV/HBV coinfection (most of them carrying 3TC-resistant HBV) have shown, on average, 4 $\log_{10}$ declines in HBV DNA levels.[69-74] TDF and TAF have a high genetic barrier for development of resistance mutations.[1,75] For people with isolated anti-HBc positivity, some experts recommend tenofovir-based ART because of the potential risk for HBV reactivation, but the precise risk is unknown (see the Nucleos(t)ide-Sparing Regimens section below) **(CIII).** However, a regimen without TDF or TAF can be considered if the HBV DNA is undetectable and the benefits outweigh the risk of HBV reactivation **(CIII).**

The decision to use TAF/FTC versus TDF/FTC should be based upon creatinine clearance (CrCl) and an assessment of risk for nephrotoxicity and risk for acceleration of bone loss.

- Among people with CrCl ≥60 mL/min, either TAF/(FTC or 3TC) or TDF/(FTC or 3TC) can be considered.

- Among people with a CrCl 30 to 59 mL/min, a TAF/FTC regimen is preferred.

- Currently approved fixed-dose combination TAF/FTC-containing regimens for the treatment of HIV are not recommended for use among people with CrCl <30 mL/min who are not on hemodialysis. For these people, renally dosed entecavir with a fully suppressive ART regimen is recommended since entecavir without suppressive ART can lead to emergence of the HIV M184V mutation **(AIII).** Renally dosed TDF and FTC or 3TC also can be used if recovery of renal function is unlikely **(AIII).** If renally dosed TDF is used, then the CrCl needs to be monitored carefully. In people with CrCl ≥15 to 29 mL/min, ART with TAF (as a single agent) and renally dosed FTC or 3TC may be used **(AIII).** Of note, some clinicians may choose to continue full-dose FTC to allow for people with CrCl 15 to 29 mL/min to remain on fixed-dose TAF/FTC products.

- In people receiving hemodialysis, ART with either renally dosed TDF plus (FTC or 3TC) **(AII)** or TAF/FTC **(AII)** may be used. TAF and FTC do not require dose adjustment in patients receiving hemodialysis; co-formulated full-dose products may be continued and given after dialysis on the day of hemodialysis. Refer to What to Start: Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy and Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency in the Adult and Adolescent Antiretroviral Guidelines for more information.

Among people with HIV/HBV coinfection, switching from a primarily TDF-based ART regimen to single-tablet TAF/FTC/elvitegravir/cobicistat maintained or achieved HBV suppression, with improved estimated glomerular filtration rate (eGFR) and bone turnover markers.[76] Among people with HBV mono-infection, TAF 25 mg was non-inferior to TDF 300 mg based on the percentage of people with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = 0.47$). People on TAF also experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than people receiving TDF ($P < 0.0001$). Furthermore, the median change in eGFR from baseline to 48 weeks also favored TAF ($P = 0.004$).[77,78] In a randomized placebo-controlled study of HIV/HBV coinfected people (mainly Asians), TAF/FTC/bictegravir (BIC) was superior to TDF/FTC/DTG in achieving HBV DNA <29 IU/ml (63% vs. 43%, respectively; $P = 0.002$) at 48 weeks but was similar at 96 weeks (75% vs 70%, respectively; $P = 0.64$).[79] Those receiving TAF/FTC/BIC had higher HBeAg seroconversion at 96 weeks (32% vs. 15%; $P = 0.008$) and HBsAg loss was not statistically different (23% vs. 14%; $P = 0.07$). Although the data are intriguing, whether these responses are related to ethnicity, HBV genotype, or other HIV-related factors still needs to be determined.

Chronic administration of 3TC or FTC as the only active drug against HBV **is not recommended** because of the high rate of selection of HBV drug-resistance mutations **(AI).**

People receiving ART should continue HBV therapy indefinitely **(AIII)** because relapses after response can occur, particularly in those with lower CD4 counts.[1] Additionally, discontinuation of nucleos(t)ide analog therapy is associated with an HBV reactivation in approximately 30% of cases,[80,81] as well as possible decompensation of liver disease and even death.[42,82-84] If anti-HBV therapy and ART must be discontinued for people with chronic HBV, serum transaminase levels and

HBV DNA should be monitored every 6 weeks for 3 months and every 3 months thereafter while off anti-HBV agents **(AIII).** If a flare occurs, anti-HBV therapy and ART should be reinstituted and can be potentially lifesaving **(AIII).**

Some people with HIV/HBV coinfection also have chronic HCV infection. Scant information is available on the treatment of HBV/HCV/HIV coinfection. Because people with HBV/HCV/HIV coinfection appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality,[85-87] attempts should be made to treat both hepatitis viruses, if feasible. Because HBV reactivation can occur during treatment for HCV infection with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation **(AIII).**[88-91] See the Hepatitis C Virus chapter for more information.

Considerations When Using Nucleos(t)ide-Sparing Regimens

With increasing use of nucleos(t)ide-sparing regimens, HBV status must be considered before such a switch. We recommend checking HBsAg, anti-HBc, and anti-HBs prior to changing to a nucleos(t)ide-sparing regimen to avoid reactivation of an unrecognized chronic HBV infection unless evaluated within the last 3 months **(AIII).** In people with a chronic HBV infection, switching to the one-pill regimen of dolutegravir (DTG)/3TC should be avoided because 3TC is then the only active drug against HBV **(AIII).** Further, switching to long-acting cabotegravir/rilpivirine (RPV) or DTG/RPV without addition of an anti-HBV drug (TAF, TDF, or entecavir) should be avoided **(AIII).**

In people with isolated anti-HBc positivity, some experts would recommend not switching to DTG/3TC or a nucleos(t)ide-sparing regimen because there is a small risk of reactivation, but this could be considered if the benefits outweigh the risk **(CIII).**[92] In a study using data from the Veterans Aging Cohort Study, HBV reactivation occurred in 1.6% of individuals who were anti-HBc positive and HBsAg negative after switching to a nucleos(t)ide-sparing regimen.[92] The risk was 20.2% in people with a remote positive HBsAg compared to 1.0% in those without a prior positive HBsAg. In people with recovery from a past HBV infection (anti-HBc positive, anti-HBs positive), DTG/3TC or a nucleos(t)ide-sparing regimen is an option provided they maintain undetectable HIV RNA levels **(AIII).**[92] In people with prior receipt of the HBV vaccine, anti-HBs should be rechecked prior to switching to a nucleos(t)ide-sparing regimen because incident infections have been reported in such situations **(AIII).**[93]

Alternative Treatment of HBV Infection Among People With HIV Who Are Not Receiving HBV-Active ART

All people with HIV should receive ART. Among people with HIV/HBV coinfection, co-treatment is essential and recommended.[68] Pegylated interferon (IFN)-α-2a (or 2b) monotherapy is approved for HBV treatment, but it should only be used in rare cases with consultation of an expert.

Regimens That Are Not Recommended

Tenofovir (TDF and TAF), entecavir, 3TC, and FTC **should not be used alone** in the absence of a fully HIV-suppressive ART regimen because of the potential for development of HIV drug-resistance mutations **(AI).**[94,95] Other anti-HBV treatment regimens include adefovir in combination with 3TC or FTC in addition to a fully suppressive ART regimen[74,96,97]; however, data on this regimen among people with HIV/HBV coinfection are limited. In addition, compared with TDF or

TAF or entecavir, adefovir is associated with higher incidence of toxicity, including renal disease, as well as higher rates of HBV treatment failure. Therefore, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) **does not recommend** an adefovir-containing regimen for people with HIV/HBV coinfection **(AI).**

Monitoring of Response to Therapy and Adverse Events

To evaluate response, HBV DNA should be monitored at 6-month intervals **(AII).** Treatment responses are slower than responses to HIV therapy and are defined as the following for nucleos(t)ide analog therapy:

- Virologic response: undetectable HBV DNA (<10 IU/mL) by real-time polymerase chain reaction[98]

- Partial virologic response: HBV DNA ≥1 $\log_{10}$ decline, but still detectable HBV DNA at 12 months[98]

- Primary nonresponse: HBV DNA <1 $\log_{10}$ decline after 3 months[99]

See the Managing Treatment Failure section below for information on managing partial virologic response.

For people who are HBeAg positive, loss of HBeAg is also a measure of virologic response. Other markers that indicate treatment success include improvement in liver histology based on biopsy, transient elastography or other noninvasive tests; normalization of serum aminotransferases; and, in those with loss of HBeAg, the development of anti-HBe. Sustained loss of HBsAg is considered by some to be a complete response or functional cure; however, this desirable serologic response is uncommon (<1% of HBsAg-positive people without HIV per year).[1] Interestingly, after ART initiation, in some studies people coinfected with HIV and HBV have up to 20% chance of loss of HBsAg especially in the first 1 to 2 years.[100,101] For this reason, HBsAg should be checked yearly after ART initiation **(AIII)**. If HBsAg loss occurs and there is a desire to switch to a nucleos(t)ide-sparing regimen, this option may be considered as long as HIV RNA suppression is maintained.

Adverse Events

Renal toxicity with TDF, including increased serum creatinine or renal tubular dysfunction, has been observed; both increased serum creatinine and renal tubular dysfunction are more frequent among people with HIV who have underlying renal insufficiency, are older, or have been treated with TDF for prolonged periods.[102] These biochemical changes are usually reversible when TDF is discontinued or changed to TAF.[103]

Electrolytes and serum creatinine levels should be evaluated at baseline and every 6 months. Because renal toxicity may be reversible, alternative anti-HBV therapy should be used if renal toxicity occurs **(AI).** If TDF is used among people with baseline renal insufficiency, either a dose adjustment as noted in the package insert or a change to TAF with appropriate dose adjustment is required.[103] See Table 6. Dosing Recommendations in People With Renal Insufficiency for more information.

TDF has been associated with a decrease in bone mineral density (BMD). TAF is associated with less of a decrease in BMD than TDF in studies of hepatitis B treatment.[104] TAF also has been associated

with early weight gain among people with HIV although the long-term consequences of this are unclear.[105]

See [Considerations for Antiretroviral Use in Patients With Coinfection: Hepatitis B Virus/HIV Coinfection](#) in the [Adult and Adolescent Antiretroviral Guidelines](#) for more information on adverse events related to TAF and TDF.

Entecavir-associated lactic acidosis is uncommon but has been reported among people with HBV mono-infection with advanced cirrhosis.[106-108]

Immune Reconstitution Inflammatory Syndrome

Return of immune competence after ART (or after steroid withdrawal or chemotherapy) can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so-called "hepatitis flare,"[109] which constitutes immune reconstitution inflammatory syndrome (IRIS) among people with HIV/HBV coinfection. IRIS may manifest when serum aminotransferase levels dramatically increase as CD4 counts rise within the first 6 to 12 weeks after ART is started, with signs and symptoms characteristic of acute hepatitis and without another cause for the flare.[110,111] After introduction of ART, serum ALT levels should be monitored closely; some experts recommend ALT testing at 6 and 12 weeks, then every 3 to 6 months thereafter. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated INR and low serum albumin) should prompt consultation with a hepatologist **(CI).**[103]

Flares are worse among people with more severe liver disease, especially those with cirrhosis.[112] Distinguishing between drug-induced liver injury, HBV drug resistance, HBeAg seroconversion, or other causes of hepatitis (i.e., acute hepatitis caused by HAV, HCV, HDV, hepatitis E virus, Epstein-Barr virus, herpes simplex virus, or cytomegalovirus infection) and IRIS may be difficult. ART-associated hepatotoxicity may be dose dependent or idiosyncratic. Among people with HIV, the risk of ART-associated hepatotoxicity has been associated consistently with elevated pre-ART aminotransferases (ALT, AST) and the presence of HBV or HCV coinfection. In HIV/HBV coinfection, baseline elevated HBV DNA levels are predictive of hepatotoxicity.[113-116] Despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (90%) people with HIV/HBV coinfection do not have ART-associated hepatotoxicity,[117] and clinically significant hepatotoxicity (elevated direct bilirubin and INR) is rare. Aminotransferase levels return to baseline in most cases, even if the offending medication is continued.[118,119] Therefore, discontinuing ART usually is not necessary in the presence of hepatotoxicity unless the following symptoms are observed: hypersensitivity (e.g., fever, lymphadenopathy, rash), symptomatic hepatitis (i.e., nausea, vomiting, abdominal pain, or jaundice), or elevations in serum aminotransferase levels >10 times the upper limit of normal **(AIII).**[120] Liver histology also may help to differentiate drug toxicity (e.g., increased eosinophils) from viral hepatitis (e.g., portal inflammation). If aminotransferases increase >2 times the baseline level, the Panel recommends monitoring aminotransferases weekly and also obtaining bilirubin and INR until the aminotransferases begin declining **(AIII).**

Other noninfectious causes of abnormal liver tests that should be considered include use of drugs or alcohol and steatotic liver disease.[121]

Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogs is defined as primary nonresponse (HBV DNA <1 $\log_{10}$ decline) after 3 months of therapy among people who consistently adhere to HBV therapy or an increase in HBV DNA levels >1 $\log_{10}$ above nadir. In either situation, treatment failure generally is due to either drug-resistant HBV if the person is on 3TC/FTC monotherapy or to nonadherence to therapy.[1] If drug-resistant HBV is present, a change in treatment is needed **(AII).** Distinct resistance patterns exist with the different groups of anti-HBV drugs: the L-nucleosides (telbivudine, 3TC/FTC); acyclic phosphonates/nucleotides (adefovir and tenofovir); and D-cyclopentane (entecavir), which shares some resistance mutations with the L-nucleosides. Many experts will obtain HBV-resistance testing because it has value in distinguishing between nonadherence and drug resistance, evaluating people with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir.[122] However, TDF is associated infrequently with clinical resistance, although slow response has been noted, as discussed above. Addition of entecavir has led to suppression of HBV DNA among people whose response to TDF is slow.[123]

With 3TC monotherapy for HBV, the rate of developing 3TC-resistance is approximately 20% per year among people with HIV/HBV coinfection.[124] If 3TC resistance is suspected or documented, TDF or TAF should be added to the ART regimen **(AIII).**[125-127] Because people with 3TC-resistant HBV will have cross-resistance to the other L-nucleosides (FTC), and partial resistance to entecavir, those agents **should not be used** among people found to have 3TC-resistant HBV **(AI).**[128] All nucleoside analogs must be dose-adjusted for renal insufficiency per package insert guidelines and Table 6. Dosing Recommendations in People With Renal Insufficiency.

If treatment failure occurs on entecavir, TDF or TAF (with or without FTC) is recommended because of the cross-resistance that occurs with L-nucleosides (3TC, FTC) **(AI).**

People whose HBV infection initially failed to respond to pegylated IFN-α can be given nucleos(t)ide analog therapy following the recommendations previously described **(CIII).**

If treatment failure with TDF or TAF occurs, particularly in 3TC- or FTC-experienced people, entecavir may be an active alternative, especially if higher doses of entecavir can be used **(CIII).**

Declines in HBV DNA levels can be slow, especially when pretherapy HBV DNA levels are very high. HBV DNA levels usually drop quickly among people who are receiving an HBV drug with high potency and a high genetic barrier to resistance—such as tenofovir—but HBV DNA levels may still be detectable for some years.[1] Thus, in a person who is adherent to therapy with a partial virologic response to tenofovir, the drug should be continued with monitoring of HBV DNA levels **(BII).** Improved virologic response has been reported with the addition of entecavir to TDF; however, whether such "intensification therapy" is required is unclear.[129]

Special Considerations for Treating End-Stage Liver Disease

People with HIV/HBV coinfection who have end-stage liver disease (cirrhosis) should be managed as a person with HBV mono-infection with end-stage liver disease, including referral to a hepatologist **(AIII).** Among people with HIV/HBV coinfection in end-stage liver disease, IFN-α is **contraindicated (AI),** but nucleos(t)ide analogs are safe and efficacious **(AI).**[124,130,131] All people with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).[132,133]

Management of ascites includes sodium restriction (<2 g/day) and the recommended diuretic regimen is spironolactone combined with furosemide (ratio of 40 mg furosemide:100 mg spironolactone) **(AI).** All people who have had SBP and those with ascites total protein <1 g/dL should receive prophylaxis against SBP with administration of oral antibiotics, such as ciprofloxacin (500 mg/day), or trimethoprim-sulfamethoxazole (one double-strength tablet/day) **(AI).**[134]

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed on all people with cirrhosis at the time of diagnosis and then every 1 year to 2 years to identify substantial gastroesophageal varices (see the American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Guidance). People with varices require nonselective beta blockers—such as nadolol or propranolol—that are the mainstay of both primary and secondary prevention of variceal hemorrhage. Esophageal variceal banding is another preventive option, particularly for those who cannot tolerate beta blockers. Hepatic encephalopathy is treated with a 40-g protein diet and the use of nonabsorbable disaccharides—such as lactulose—and/or nonabsorbable antibiotics, such as rifaximin.[1]

Because people with HBV-related cirrhosis are at increased risk of HCC,[135] imaging studies with alpha fetoprotein should be performed every 6 months, as recommended in HBV mono-infection **(AI).**[1] Choice of imaging (ultrasound, computed tomography, or magnetic resonance imaging) depends upon the expertise of the imaging center. Usually, ultrasound is the initial preferred imaging modality.[1]

People with HIV/HBV coinfection with decompensated liver disease and/or early HCC are candidates for liver transplantation. HIV infection is not a contraindication to organ transplantation among people on suppressive ART.[136] Because transplantation does not cure HBV infection, post-transplant hepatitis B immune globulin (HBIG) and HBV treatment is required **(AII).** People with HIV who are potential candidates for liver transplantation should be referred to a liver specialist for further evaluation.

Preventing Recurrence

As previously indicated, most people should continue HBV therapy with nucleos(t)ide analogs indefinitely **(AIII)** because relapses after response can occur, particularly in those with lower CD4 counts, and because reports of hepatitis flares after discontinuation of 3TC in those who have not reached treatment endpoints can be extrapolated to other HBV-active drugs.[82-84]

Special Considerations During Immunosuppressive Therapy

With immunosuppressive therapy, both in the context of malignancy and rheumatologic/autoimmune diseases, reactivation of HBV infection can occur. HBV reactivation in people without HIV with HBsAg-positive/anti-HBc-positive disease receiving immunomodulatory therapy is well described, especially with anti-CD20 antibodies.[137-139] Even among people with HBsAg-negative/anti-HBc-positive disease, HBV reactivation occurs in up to 18% of people receiving anti-cancer drugs[140] and 1.7% of people receiving rheumatologic disease drugs.[141]

If not already performed, people with HIV undergoing immunosuppressive therapy should have HBsAg, anti-HBc, and anti-HBs testing. People who are HBsAg positive should receive treatment with TDF or TAF plus 3TC or an FTC-based ART regimen (see Preferred Regimens above) **(AII).** The optimal approach for those people with HBsAg-negative/anti-HBc positive disease is unknown.

However, because TDF or TAF plus FTC or 3TC is a preferred backbone for ART, it is prudent to start or modify ART to include these drugs before initiating immunosuppressive, cytotoxic, or immunomodulatory therapy among people with HBsAg-negative/anti-HBc-positive disease **(BIII).** If TDF or TAF/FTC or 3TC cannot be used as part of their HIV regimen, these people either could receive entecavir for anti-HBV prophylaxis or could be monitored and given entecavir if signs of HBV reactivation occur (increase in HBV DNA or HBsAg seroreversion) **(BIII).** The option to give pre-emptive entecavir prophylaxis (in the presence of a fully suppressive ARV regimen) is preferred if HBV DNA is detectable or if immunosuppression is more severe, such as with anti-CD20 antibodies **(AII).**[139] No studies have been performed on the appropriate length of therapy, but the Panel agrees with the AASLD 2018 Hepatitis B Guidance recommendation to continue treatment for 6 months after cessation of immunosuppressive therapy and for 12 months in the setting of anti-CD20 antibodies **(BIII).**[1]

Special Considerations During Pregnancy

Pregnant people with HIV should be screened for HBV infection, which may be first diagnosed at this time **(AI).**[59] In the interest of completing adult HBV screening, prenatal visits are an opportunity to offer the triple panel to a pregnant person and link the patient to care or vaccinate as needed. People with HIV should be tested for HBsAg during each pregnancy, preferably in the first trimester, even if vaccinated or tested previously.[18,59] Pregnant people with a history of appropriately timed triple panel screening and without subsequent risk for exposure to HBV (i.e., no new HBV exposures since triple panel screening) only need HBsAg screening. Testing pregnant persons known to be chronically infected or immune enables documentation of the HBsAg test result during that pregnancy to ensure timely prophylaxis for exposed infants (see below). Those who are both HBsAg negative and anti-HBs negative should be offered vaccination against HBV **(AII)**. Pregnant people with chronic HBV infection who have not already received the HepA vaccine series should be screened for immunity to HAV infection. Those who screen negative for total anti-HAV should receive the HepA vaccine series **(AIII).**[142] Treatment of symptomatic acute HBV infection during pregnancy is supportive, with special attention given to maintaining blood glucose levels and normal clotting status. High maternal HBV DNA levels correlate strongly with perinatal HBV transmission, including failures of HBV passive-active immunoprophylaxis.[143-146] See Hepatitis B Virus/HIV Coinfection in the Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States.

ART—including drugs active against both HIV and HBV—is recommended for all people with HIV/HBV coinfection, including pregnant people **(AII).** TAF or TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone for pregnant people with chronic HBV infection **(AIII).**[142] Entecavir has not been well evaluated in pregnancy, with too few exposures to assess overall risk; thus, it is **currently not recommended** for pregnant people with HBV/HIV coinfection **(AIII).**[142]

Cases of adverse events during pregnancy related to any of the antiretroviral or anti-HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263 or SM_APR@APRegistry.com). As of June 2024, 5,684 cases of pregnancy outcomes after first-trimester exposures to 3TC have been reported to the Antiretroviral Pregnancy Registry, with no indication of an increased risk of birth defects after exposure (see *The Antiretroviral Pregnancy Registry Interim Report*). 3TC has been well tolerated by pregnant people and is a recommended NRTI for use in pregnancy **(AII).**[147] Similarly, no increase in birth defects has been noted in 5,030 cases of first-trimester exposure to FTC. FTC is a recommended NRTI and is used commonly

in pregnancy **(BII).**[148] A total of 5,014 cases of first-trimester exposure to TDF and 1,242 cases of first-trimester exposure to TAF have been reported to the Antiretroviral Pregnancy Registry with no increase in birth defects noted.[148]

Several large studies have been conducted to evaluate the effect of tenofovir use in pregnancy. No evidence exists that the use of TDF increases the risk of birth defects. Overall, the available evidence does not indicate a link between maternal TDF use and infants who are low birth weight or small for gestational age. Some concern remains regarding a link between maternal TDF use and preterm birth,[149] but the evidence is mixed; the role of concomitant medications and other cofactors and/or confounders requires further investigation.[147]

Infants born to people who are HBsAg positive should receive HBIG and HepB vaccine (first dose of three) within 12 hours of delivery **(AI).** The second and third doses of vaccine should be administered at 1 to 2 months and 6 months of age, respectively **(AI).** Infants who weigh <2,000 g at birth should receive HBIG and four doses of HepB vaccine; administer one dose of HepB vaccine within 12 hours of delivery and initiate the three-dose HepB vaccine series beginning at age 1 month (four doses total: birth, 1 month, 2–3 months, and 6 months).

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Hepatitis C Virus Infection

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Epidemiology

Prevalence and Incidence Estimates

Hepatitis C virus (HCV) is an enveloped, single-stranded RNA virus of the Flaviviridae family with seven known genotypes and 84 subtypes, with genotypes 1 and 3 being most common worldwide.[1-3] It is the most commonly reported bloodborne infection in the United States and is a leading cause of liver-related morbidity and mortality, particularly among people with HIV. In 2019, the estimated global prevalence of chronic HCV infection was 58 million (0.8% of general population), a decline from previous estimates of 71 million in 2015.[4] In the United States, updated estimates for 2013 to 2016 are that approximately 4.1 million people were HCV antibody positive (past or current infection; 1.7% of all adults); 2.4 million were HCV RNA positive (current infection; 1% of all adults).[5] Comparable data from 2003 to 2010 showed that 4.6 million people were antibody positive and 3.5 million were living with current HCV infection.[6] These updated lower prevalence estimates reflect interval trends, including increased cures with new treatment options and increasing death rates due to aging. However, these may be offset by increases in incident cases due to the opioid crisis in vulnerable counties.[7,8] Despite variable state-level surveillance practices,[9] Centers for Disease Control and Prevention (CDC) surveillance data from 2019 show regional differences in incidence and prevalence, increasing rates in rural areas, ongoing racial/ethnic disparities, and changing demographics, including a bimodal distribution of infections with peaks at 29 years and at 59 years of age.[10] Attributable mortality is highly variable among states and counties.[11]

Given the shared transmission routes between HIV and HCV, estimates of the burden of HCV infection in people with HIV (HIV/HCV coinfection) have been highly variable depending on the comprehensiveness of databases analyzed. A global systematic review and meta-analysis of studies published between 2002 and 2015 estimated that there were 2.3 million cases of coinfection worldwide, with 1.3 million (58%) attributed to persons who inject drugs; this translates to HCV coinfection prevalence of 6.2% among people with HIV.[12] Compared with people without HIV, the odds of HCV infection in people with HIV are six times higher. The prevalence of HCV infection among people with HIV is distributed in the following subgroups: people who inject drugs (82.4%), men who have sex with men (MSM, 6.4%), and those who are pregnant or heterosexually exposed (2.4%).[12] Estimates of HCV coinfection in the United States[10] have been cited as 21% but have ranged from 6% to 30% with high variability based on the distribution of HIV transmission risk factors.[13,14] In the United States, it is estimated that 62% to 80% of people who inject drugs who have HIV also have HCV infection.[10]

The availability of highly effective treatments for HCV infection has led to national and global initiatives aimed at HCV elimination in general and in high-risk persons, such as those with HIV coinfection. The World Health Organization has developed targets for countries to achieve HCV elimination by 2030: diagnosing 90% of those with chronic infection and curing 80% of those diagnosed.[4] The CDC *Division of Viral Hepatitis 2025 Strategic Plan* aims to increase HCV cure to >85% by 2030.[15] The use of an HCV cascade of care has shown that there are ongoing gaps to attaining cure encompassing screening, initiating and completing treatment, and preventing

reinfection.[16,17] Worldwide, 15.2 million (26.2%) out of an estimated 58 million people knew their HCV status by the end of 2019.[18] With progress in direct antiviral treatments, 9.4 million people received HCV treatment, with the vast majority cured, between 2015 and 2019.[18] Micro-elimination efforts to scale-up treatment as prevention among people with HIV have successfully demonstrated that such efforts can decrease hepatitis C incidence.[19-24]

Transmission Routes

Both HIV and HCV can be transmitted by percutaneous exposure to blood or blood products, sexual intercourse, and perinatal transmission; however, the relative efficiency of transmission by these routes varies substantially.[25] HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures and has been shown to survive for weeks in syringes.[26,27] Transmission via injection drug use remains the most common mode of acquisition in the United States, while transmission through contaminated blood products is now rare. Health care–associated transmission of HCV also can occur because of improper reuse of parenteral medications and equipment.[28] Other factors that have been associated with HCV infection include accidental occupation-related needlestick injuries, intranasal cocaine use, chronic hemodialysis, and tattoo placement.

Multiple outbreaks of acute HCV infection in MSM demonstrate that sexual transmission is an important mode of acquisition in this population. Risk factors include unprotected receptive anal intercourse, use of sex toys, non-injection recreational drug use, and concurrent sexually transmitted infections (STIs).[29-32] Evidence for increasing HCV incidence and prevalence in HIV-negative men seen in HIV pre-exposure prophylaxis (PrEP) clinics has led to current recommendations to monitor for acute HCV infection and routinely test for HCV as part of PrEP care.[33-35] Heterosexual transmission of HCV is uncommon but more likely in those whose partners have HIV/HCV coinfection.[16,36-38]

Perinatal transmission of HCV infection occurs in approximately 7% and 12% of infants born to HCV-seropositive and RNA-positive mothers without and with HIV,[39-41] respectively, with possible decreased transmission risk for women with HIV receiving antiretroviral treatment.[42]

Clinical Manifestations

Both acute and chronic HCV infections are usually minimally symptomatic or asymptomatic. Fewer than 20% of patients with acute infection have characteristic symptoms, including low-grade fever, mild right-upper-quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Unexplained elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels may be the only laboratory finding during acute and chronic infection. Recognition of acute HCV infection in patients with new-onset liver enzyme elevations is clinically important; early initiation of HCV treatment can lower the likelihood of poorer outcomes and prevent transmission to others (treatment as prevention).[43-45]

Cirrhosis develops in 20 to 40% of patients with chronic HCV infection within 20 years after infection, although the risk for an individual is highly variable.[46-48] Risk factors for development of significant liver disease include older age at the time of infection, male sex, obesity, and concomitant alcohol use.[47,49] HIV coinfection adversely affects the course of HCV infection, resulting in significantly accelerated progression of liver disease to cirrhosis, particularly in those with advanced immunodeficiency[50,51] (CD4 T lymphocyte [CD4] count <200 cells/mm^3). Further, coinfected patients with cirrhosis progress more rapidly to life-limiting outcomes—such as end-stage liver

disease and hepatocellular carcinoma (HCC)—than those who are HCV mono-infected,[52,53] even if they are virally suppressed.[54] Because of its high prevalence and accelerated progression, HCV infection was a leading non-AIDS cause of death in people with HIV before the advent of highly effective direct-acting antivirals.[55-57] In addition to liver disease, HCV may be associated with symptomatic vasculitis due to cryoglobulinemia (largely affecting the skin or joints), renal disease (membranoproliferative glomerulonephritis), and porphyria cutanea tarda.

Diagnosis

On entry into HIV care, all patients should undergo routine HCV screening **(AII).** Initial testing for HCV should be performed using a U.S. Food and Drug Administration (FDA)-approved immunoassay licensed for detection of antibody to HCV (anti-HCV) in blood.[58,59] For at-risk HCV-seronegative individuals, specifically MSM or persons who inject drugs, HCV antibody testing, using an FDA-approved immunoassay, is recommended annually or as indicated by clinical presentation, risk activities, or exposure **(AII).** Concordantly, both the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV guidance and CDC PrEP guidelines also recommend HCV serologic testing at baseline and every 12 months for MSM, transgender women, and people who inject drugs.[59,60] Nucleic acid testing for HCV RNA is recommended in settings where acute infection is suspected or in persons with known prior infection cleared spontaneously or after treatment **(AIII).**

False-negative anti-HCV antibody results are possible among people with HIV but uncommon (2% to 4%), and more likely to be seen in patients with advanced immunosuppression[61] (CD4 cell count <200 cells/ mm^3). HCV RNA testing should be performed in those patients with risk factors or unexplained ALT elevation. In addition, negative anti-HCV antibody results can occur during acute infection. Following acute HCV infection, the duration of the window period prior to seroconversion is highly variable, ranging from 2 weeks to more than 24 weeks,[62,63] with antibody response in most persons detectable at 8 to 12 weeks. Serum ALT levels are frequently elevated early in the course of HCV infection, and high ALT levels should prompt testing for HCV RNA if serologic test results are negative or indeterminate in individuals at risk of HCV infection.[64]

Individuals who test positive for HCV antibody should undergo additional diagnostic testing by using a sensitive quantitative assay to measure plasma HCV RNA level and confirm current infection **(AI).** This should preferentially be done as an automatic reflex to HCV RNA testing of the leftover serum from the blood draw for antibody testing to facilitate diagnosis.[65] Reinfection can occur in both seropositive individuals who spontaneously clear their infection or those who achieve a sustained virologic response to treatment. Diagnosing a new active infection will require HCV RNA testing in such individuals **(AII).**

Preventing Exposure

The primary route of HCV transmission is blood-to-blood contact, most commonly from sharing drug-injection equipment or paraphernalia (i.e., "cookers," filters, or water) previously used by an infected person with HCV. Prevention approaches for persons who inject drugs include harm-reduction encompassing opioid agonist therapy and syringe services programs to avoid the reuse or sharing of syringes, needles, water, cotton, and other drug preparation equipment.[66,67] Both needle and syringe exchange programs and opioid substitution therapy have been shown to reduce the risk of HCV acquisition in people who inject drugs.[67,68] HCV also can be transmitted sexually, especially among MSM with HIV.[69] Risk factors for sexual HCV acquisition include unprotected anal receptive

intercourse, fisting, sharing of sex toys, ulcerative STIs, and use of methamphetamine or other sex-enhancing drugs (injection or otherwise).[70,71]

Patients should be counseled regarding the risk of sexual HCV acquisition **(AII).** Those with multiple sex partners or STIs should be advised to use barrier protection to reduce their risk of STIs including hepatitis C infection **(AII).**

Preventing Disease

There is no available vaccine or recommended post-exposure prophylaxis to prevent HCV infection.[72,73] Following acute HCV infection, chronic infection can be prevented within the first 6 to 12 months after infection through antiviral treatment; high rates of viral clearance have been observed with HCV treatment during the acute phase of infection.[74,75]

Because most patients with acute HCV infection may transmit to others and are at risk for loss to follow-up, immediate treatment with the same regimens recommended for chronic HCV should be offered **(AIII).**[44,76] Specific treatment regimens in acute infection are the same as those recommended for chronic HCV infection and are detailed in the Treating HCV section.

People with HCV infection should be tested for previous or concurrent hepatitis B virus (HBV) infection because coinfection with HBV is associated with increased morbidity **(AII).** Those without evidence of immunity to HBV infection should be vaccinated (see the Hepatitis B Virus Infection section) **(AII).** Likewise, because acute hepatitis A virus (HAV) infection is more likely to be fulminant in persons with HCV infection,[77] these patients should be screened for immunity (HAV immunoglobulin G or antibody total) and non-immune persons should be vaccinated **(AII).**

People with HCV infection should be counseled about methods to prevent liver damage by avoiding any alcohol consumption (because alcohol accelerates progression of liver disease), limiting ingestion of potentially hepatotoxic medications (e.g., acetaminophen should be limited to <2 g/day for those with acute infection or bridging fibrosis/cirrhosis), and avoiding iron supplementation in the absence of documented iron deficiency.[78]

People with HIV/HCV coinfection with cirrhosis are at risk of life-threatening complications and should be managed in consultation with a gastroenterologist or hepatologist. In particular, individuals with cirrhosis should undergo serial screening for HCC; current guidelines recommend performing ultrasonography at 6-month intervals, although the optimal screening strategy is unknown **(AIII).**[79] Because of its relatively poor specificity and sensitivity, serum alfa-fetoprotein is an adjunct to ultrasonography but should not be the sole screening method.[79] HIV infection is not a contraindication to liver transplantation; accordingly, coinfected patients with decompensated liver disease and/or early HCC may be considered for transplantation at specialized transplant centers.

Although earlier studies focused on the potential for antiretroviral (ARV)-associated liver injury with certain agents, more recent studies have found that effective HIV treatment is associated with reduced risk of liver disease progression, though not to levels of persons with HCV infection without HIV.[54,80] Coinfected patients should be treated in accordance with the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.

Treating HCV Infection

Introduction

Direct-acting antiviral (DAA) regimens for HCV infection have become standardized with one of two pangenotypic, highly efficacious and well-tolerated antiviral treatment regimens, which are the preferred therapy for HCV infection for almost all persons with HIV and HCV. Clinicians can refer to the most recent AASLD/IDSA HCV treatment guidance.

The goals of therapy, treatment regimen, and monitoring parameters for patients with HIV/HCV coinfection are similar to those recommended for patients with HCV mono-infection. However, people with HIV were historically considered a "special population" with regard to HCV treatment. This designation was rooted in inferior responses to interferon-based treatment for those with HIV.[81,82] The arrival of initial DAA regimens narrowed the gap in response to treatment but continued to present significant drug–drug interaction considerations and, in some circumstances, warrant extended treatment durations.

Simplified approaches to HCV treatment have emerged as a means to facilitate treatment by non-specialist providers and increase treatment uptake for the majority of persons with HCV infection. In general, simplified approaches to HCV treatment apply to treatment-naive persons without cirrhosis and encompass minimal baseline testing (with omission of genotype), standardized treatment approaches using pangenotypic regimens, no on-treatment testing or in-person follow-up, and limited follow-up to confirm sustained virologic response (SVR).

Several factors now allow the inclusion of people with HIV in simplified HCV treatment recommendations. The emergence of unboosted integrase strand transfer inhibitor (INSTI)-based ARV regimens has eliminated clinically significant drug interactions with current first-line DAA regimens. Additionally, the improved safety profile of tenofovir alafenamide (TAF) combined with safety data in the setting of boosted ARV regimens during coadministration with DAAs obviate the need for enhanced toxicity monitoring for people with HIV in most instances. Finally, accumulation of clinical efficacy data and the necessity of expanding treatment access support the use of simpler standardized treatment approaches initially validated in HCV mono-infected populations for those with HIV. Based on these developments and the emergence of pangenotypic DAA regimens, treatment of HCV can be approached using simplified protocols for the majority of people with HIV.

Published clinical trial data directly support a simplified approach to HCV treatment, including for people with HIV. The AIDS Clinical Trial Groups (ACTG) A5360 study (MINMON) evaluated an approach consisting of limited baseline testing and supply of the entire 84-tablet (12-week) sofosbuvir/velpatasvir treatment regimen in 399 participants, including 166 with HIV.[83] All participants were HCV treatment-naive, compensated cirrhosis was allowed, and no pre-treatment HCV genotyping was performed. No on-study laboratory monitoring or in-person follow-up was conducted. The SVR after 12 weeks post-treatment (SVR12) was 95% overall (95% CI, 92.4% to 96.7%) and 95% in the subset of people with HIV (157/166).

The SMART-C study randomized participants to either a standard 8-week treatment with glecaprevir/pibrentasvir (n = 127), which included in-person follow-up at weeks 4 and 8 with medication refill required at week 4, or to a simplified approach (n = 253) that omitted the on-treatment visits with all medication dispensed at initiation.[84] Persons with previous HCV treatment or cirrhosis were excluded and only a small number of people with HIV (n = 27) were included. A

modified intention-to-treat analysis (excluding lost to follow-up and missing SVR12 results) established non-inferiority of the simplified approach with SVR12 of 97% (233/241) compared with 98% (121/123) in the standard-approach arm. No difference in response was seen by HIV status.

Staging and Monitoring

While a pre-HCV treatment assessment of patient readiness for therapy should be completed, with an indication that reasonable adherence can be expected, HCV DAA therapy should not be withheld solely due to perceived lack of adherence with HIV therapy or untreated HIV infection **(BIII).** Evidence suggests the level of adherence needed for HCV cure is more modest than that required to maintain HIV viral suppression.[85-87] In addition, despite a lack of HIV control, patients may be uniquely motivated by the potential for HCV cure, thereby increasing the likelihood of successful treatment.

Additional fibrosis stage assessment may be indicated in people with HIV with an indeterminate FIB-4 (1.45–3.25) score, particularly if cirrhosis is suspected **(BIII).** Additional blood- or serum-based assays for fibrosis staging **are not recommended** because they provide little benefit over FIB-4 **(BII).**[88,89]

Non-invasive ultrasound-based (e.g., shear wave elastography or vibration controlled transient elastography) or imaging-based (e.g., magnetic resonance elastography) modalities are recommended if available **(BII).** Liver biopsy **is no longer recommended** for liver fibrosis staging related to HCV infection unless there is another indication to obtain one **(AII).** Treatment should not be withheld if access to additional staging modalities is not readily available **(AIII).**

Simplified Approach to HCV Treatment

The current AASLD/IDSA HCV guidance for simplified HCV treatment of treatment-naive adults (without cirrhosis or with compensated cirrhosis) excludes persons with HIV. The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommends an approach that allows most people with HIV to qualify for simplified HCV treatment. This simplified approach is appropriate except in certain people with HIV with conditions noted in **Box 1.** Such exclusions highlight the importance of particular ARV regimens with significant drug–drug interactions with ARVs (see below).

Box 1. Characteristics of People with HIV for Whom Simplified Hepatitis C Virus Treatment Is Not Recommended[a]

1. Prior HCV treatment (Reinfection after prior successful therapy is **not** an exclusion.)

2. Decompensated cirrhosis[b]

3. TDF-containing regimen with an eGFR <60mL/min

4. On efavirenz, etravirine, nevirapine, or boosted HIV-1 protease inhibitors[c]

5. Untreated chronic HBV infection

6. Pregnancy

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[a] People with HIV and HCV infection who meet these exclusion criteria should be treated for HCV following standard approaches (see the AASLD/IDSA HCV Guidance).

[b] Including, but not limited to, current or prior variceal bleeding, ascites, or hepatic encephalopathy

People with HIV on boosted protease inhibitors are not eligible for treatment with glecaprevir/pibrentasvir and may require on-treatment monitoring.

Key: eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; TDF = tenofovir disoproxil fumarate

A limited pre-treatment assessment for people with HIV is essentially the same as for people without HIV who qualify for a simplified approach **(Box 2) (AIII).** Key components are documentation of active HCV infection and initial assessment of liver fibrosis stage. Determination of HCV genotype prior to treatment is not necessary in treatment-naive patients, with the exception of persons with compensated cirrhosis who are planned for treatment with sofosbuvir/velpatasvir. In this case, if genotype 3 HCV infection is identified, additional testing for resistance-associated substitution (RASs) is required before treatment with sofosbuvir/velpatasvir. Notably, HIV parameters (i.e., HIV RNA or CD4 count) are not required to determine eligibility for a simplified approach. The efficacy of HCV DAA treatment for people does not appear to be compromised at lower CD4 counts.[90-92]

Box 2. Pre-treatment Assessment Under Simplified Approach

1. Creatinine, liver function tests, and complete blood count

2. HCV RNA

3. Hepatitis B surface antigen

4. Initial fibrosis staging with FIB-4 (FIB-4 calculator)[a]

5. Medication and drug interaction review

6. HCV genotype required if cirrhosis is present

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[a] Additional testing may be required if results are indeterminate (see text).

Key: HCV = hepatitis C virus

Drug–Drug Interactions

Drug interactions with ARVs pose less of a constraint on DAA use to treat HCV infection in people with HIV given the prominence of unboosted INSTI and TAF among first-line ARV regimens.[93] A comprehensive review of drug interactions between ARVs and antivirals for hepatitis C can be found within the Hepatitis C Virus/HIV Coinfection section of the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Interactions of clinical significance pertaining to the recommended DAA regimens are highlighted here and in **Table 4**.

Efavirenz coadministration results in a significant decrease in glecaprevir, pibrentasvir, and velpatasvir exposures.[94,95] People with HIV on an efavirenz-containing regimen are not eligible for simplified DAA treatment approaches **(Box 1)** and generally require an ARV switch prior to DAA treatment **(AII).**

Given similar pharmacologic profiles, including cytochrome P450 (CYP) enzyme induction, nevirapine and etravirine are also not recommended for coadministration with HCV DAAs, including glecaprevir/pibrentasvir and sofosbuvir/velpatasvir **(AII).**

Ritonavir- or cobicistat-boosted protease inhibitors significantly increase glecaprevir and pibrentasvir exposure[94]; people with HIV on boosted protease inhibitor (PI)–based ARV regimens were not included in registrational trials of glecaprevir/pibrentasvir and coadministration is not

recommended **(BII).**[96] Boosted protease inhibitors also increase velpatasvir exposure, which in turn increases tenofovir plasma exposure particularly when administered as TDF.[95] People with HIV on boosted ARV regimens were included in sofosbuvir/velpatasvir registrational trials, and the combination was not associated with increased adverse events.[97]

Given these considerations, sofosbuvir/velpatasvir can be co-administered with boosted ARV regimens **(AII);** TAF-based regimens are preferred. People on TDF-containing boosted ARV regimens are not eligible for simplified HCV treatment if their estimated glomerular filtration rate is <60 mL/min because monitoring on treatment is recommended **(AII).**

Summary of Major Drug Interactions Between HIV and HCV Antivirals

HIV Antivirals	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir
EFV, ETR, NVP, and other strong CYP 3A4 and P-gp inducers	Significant decrease in glecaprevir and pibrentasvir concentrations **(avoid)**	Significant decrease in velpatasvir concentrations **(avoid)**
PI/r, PI/c, unboosted ATV	Significant increase in glecaprevir and pibrentasvir concentrations **(avoid)**	Boosted PIs may increase velpatasvir concentrations, but no significant adverse events in clinical trial Coadministration allowed
TDF, TAF	Coadministration allowed	TAF preferred If TDF is used with boosted PIs if GFR <60 mL/min, monitoring is recommended.
RPV, DOR, EVG/c, RAL, BIC, DTG, ABC, FTC, 3TC, MVC	Coadministration allowed	Coadministration allowed

Key: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CYP = cytochrome P450; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GFR = glomerular filtration rate; FTC = emtricitabine; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; P-gp = p-glycoprotein; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

HCV Treatment Regimens

In HCV treatment-naive persons **without cirrhosis,** the recommended DAA regimens are either—

- Glecaprevir/pibrentasvir fixed dose combination (FDC) (100-mg/40-mg tablet), three tablets daily for 8 weeks **(AI)**

OR

- Sofosbuvir/velpatasvir FDC (400-mg/100-mg tablet), one tablet daily for 12 weeks **(AI)**

As noted in **Box 1,** these recommendations do not apply to HCV treatment–experienced patients because some of these individuals may require other DAA combinations and/or consultation with an expert. Persons meeting other criteria listed in **Box 1** should be treated according to standard approaches. Clinicians can refer to the most recent HCV treatment guidance for recommendations.

Primary data supporting the efficacy and safety of the two recommended treatment regimens in people with HIV come from registrational trials. In the ASTRAL-5 study, 12 weeks of sofosbuvir/velpatasvir without ribavirin was given to 106 people with HIV, including 19 with cirrhosis.[97] The SVR12 was 95% by intention-to-treat analysis with only two of five failures due to confirmed viral relapse. All participants with cirrhosis were cured. The EXPEDITION-2 study evaluated glecaprevir/pibrentasvir 300 mg/120 mg in 153 people with HIV with duration determined by cirrhosis status, with 137 non-cirrhotic participants treated for 8 weeks and 16 with cirrhosis treated for 12 weeks.[96] By intention-to-treat analysis, SVR12 was 98%, including 135 out of 137 participants without cirrhosis and 15 out of 16 participants with cirrhosis. The only confirmed virologic failure was virologic breakthrough at week 8 in a participant with genotype 3 and cirrhosis. Both regimens were well tolerated with low rates of discontinuation and no severe treatment-associated adverse events.

If compensated cirrhosis is present and sofosbuvir/velpatasvir is the planned regimen, then pre-treatment HCV genotyping is recommended **(AII).** If HCV genotype 3 is identified, NS5A resistance testing and modification of the sofosbuvir/velpatasvir regimen or selection of an alternative therapy may be necessary (for a full discussion, see the HCV treatment guidance). For all other genotypes or if glecaprevir/pibrentasvir is being used (regardless of genotype), no modification to the treatment regimen is required in the setting of compensated cirrhosis **(AIII).** The lower-strength recommendation for use of 8 weeks of glecaprevir/pibrentasvir in the setting of cirrhosis stems from a lack of prospective trials evaluating this duration in people with HIV and cirrhosis; 12 weeks of glecaprevir/pibrentasvir may be used in this setting **(CI).** The EXPEDITION-8 trial evaluated 8 weeks of glecaprevir/pibrentasvir in 343 participants with compensated cirrhosis and without HIV.[98] The intention-to-treat SVR12 was 98% and >99% in a per protocol analysis. The lone virologic failure was in genotype 3 infection yielding a per protocol SVR12 in this group of 98% (60/61). Data from real-world experience of use of 8 weeks of glecaprevir/pibrentasvir in the setting of cirrhosis were recently presented and included a small number of people with HIV.[99] Of the 20 people with HIV treated for 8 weeks, 19 out of 20 achieved SVR with no confirmed virologic failures.

Specific Treatment Situations

Acute HCV Infection Treatment

People with HIV are at risk for acute HCV infection. Given the public health implications in reducing onward transmission, in addition to benefit for the individual, HCV treatment should be started as soon as possible in this population **(AIII).**[21,44,100] The simplified treatment regimens outlined above are recommended in acute HCV infection **(AII);** shorter durations of therapy are currently being investigated. Patients who achieve viral clearance either spontaneously or after treatment should be counseled about the potential for reinfection.

Prior DAA Failure Retreatment

Despite the high cure rates associated with current DAA regimens, the large number of DAA treatments will inevitably result in an appreciable number of DAA failures. Persons with HIV were not included in the registrational trial of sofosbuvir/velpatasvir/voxilaprevir for retreatment of HCV infection[101]; nor were they included in initial prospective trials of either glecaprevir/pibrentasvir or sofosbuvir plus glecaprevir/pibrentasvir for HCV treatment of prior NS5A inhibitor containing DAA failures.[102,103] A follow-up prospective study comparing 12 weeks versus 16 weeks of

glecaprevir/pibrentasvir for genotype 1 sofosbuvir plus NS5A inhibitor failures did include a small number of people with HIV (~5%).[104] Similarly, published real-world experiences with retreatment of prior DAA failures are underrepresented with respect to people with HIV (all <5% except one with 15%).[105-108]

Drawing on the experience with initial DAA therapy of HCV infection, where people with HIV have nearly identical outcomes to persons with HCV infection alone, treatment approaches for DAA failures should be the same as those for persons with HCV mono-infection **(AIII).** Clinicians should refer to the most recent HCV treatment guidance for up-to-date recommendations.

Laboratory Monitoring and Post-Treatment Follow-Up

Laboratory monitoring while on treatment is not required for patients qualifying for the simplified treatment approach. However, documentation of HCV RNA levels at week 4 of therapy may be required by some payors prior to providing additional refills needed to complete therapy.

Effort should be made to document SVR (HCV RNA less than lower limits of quantification) at least 12 weeks after completion of therapy **(AI).** Patients without cirrhosis who achieve SVR do not require continued liver disease monitoring.

Periodic assessment for HCV reinfection should be done via HCV RNA testing on an at least yearly basis for those with ongoing risk behaviors or more frequently as dictated by clinical circumstances (e.g., new STI diagnosis or elevated liver enzymes) **(AII).**

In the setting of cirrhosis, hepatocellular carcinoma screening with liver ultrasound every 6 months should continue indefinitely **(BII).**

Special Considerations During Pregnancy

Pregnant individuals, including those with HIV, should be tested for HCV infection to allow appropriate management for the mothers during pregnancy and after delivery and also to ensure their infants are identified as at risk for transmission and monitored **(AIII).**[109]

The rate of perinatal transmission has been reported at approximately 7% for infants born to mothers without HIV and 12% for infants born to mothers with HIV.[35,39,110] Due in large part to the opioid epidemic, more infants are born today to pregnant people with HCV infection than ever before[111,112]; thus, universal screening for pregnant people during each pregnancy, regardless of HIV status, is now the standard of care.[113] For the care of the infant, knowledge of exposure risk allows for screening for perinatal transmission.[114] For the pregnant person, harm-reduction counseling and linkage to HCV care and treatment are important.[115]

Assessments for liver disease stage can be delayed until pregnancy related and postpartum changes have resolved. Individuals with known cirrhosis are at higher risks of complications during pregnancy, both for the individual and their infant. Hepatitis A and hepatitis B vaccines can be administered during pregnancy, and individuals who have not previously been vaccinated should receive them **(AII).**

Data are limited regarding the role of medical or surgical interventions to reduce the risk of perinatal HCV transmission. Nearly all studies, including those in individuals with and without HIV, have found that elective cesarean delivery does not reduce the risk of perinatal HCV transmission.[116-119]

Moreover, there is an increased risk of maternal morbidity associated with cesarean compared with vaginal delivery, particularly in the setting of maternal HIV infection.[120-123] Thus, while elective cesarean delivery in individuals with HIV/HCV coinfection can be considered based on HIV-related indications, data do not support its routine use for the prevention of HCV transmission.

The current standard of care for treatment of HCV infection, regardless of duration, is DAA combination therapy. In real-world studies, SVR rates are similar to those from registration trials,[124,125] and are consistently >90%. DAAs have not been sufficiently studied in pregnant women with HCV infection. In a pilot study of ledipasvir/sofosbuvir in pregnant women (without HIV), treatment was started in the end of the second/beginning of the third trimester and found to be safe and resulted in cure in nine women.[126] Pharmacokinetic measurements did not identify clinically significant changes.

Historically, while not studied in this population, DAA drugs have not demonstrated significant fetal toxicity concerns in animal studies, in contrast to when interferon and ribavirin were the standard of care. Interferon is no longer used for the treatment of HCV infection and ribavirin is used infrequently and usually in complex treatment or retreatment scenarios. Ribavirin is an FDA category X drug because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia.

Ribavirin **should not be used** during pregnancy **(AII).** Women of childbearing potential and men receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy **(AIII).** Inadvertent pregnancy during paternal exposure was not associated with adverse events in two newborns.[127] For now, treatment with DAA during pregnancy **is not recommended (CIII);** more safety data are needed.

Recommendations for Treatment of Hepatitis C Virus Infections

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For Treatment-Naive Patients Without Cirrhosis (Any Genotype or No Pre-Treatment Genotype)

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks **(AI)** *or*

- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks **(AI)**

Note: Characteristics that exclude people with HIV from receiving simplified therapy are outlined in **Box 1.**

For Treatment-Naive Patients with Compensated Cirrhosis (Recommendations Based on Genotypes)

Genotypes 1, 2, 4–6

Preferred Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks **(AIII)** *or*

- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks **(AI)**

Alternative Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 12 weeks **(CI)**

Genotype 3

Preferred Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks **(AIII)**

Alternative Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 12 weeks **(CI)** *or*

- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily, with or without ribavirin for 12 weeks pending results of NS5A RAS testing **(CI)**

For Treatment of Acute HCV Infection

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks **(AII)** *or*

- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks **(AII)**

Recommendations for treatment after DAA failure are not provided; see the corresponding section in the AASLD/IDSA HCV treatment guidance.

Key: AASLD = American Association for the Study of Liver Diseases; DAA = direct-acting antivirals; FDC = fixed-dose combination; HCV = hepatitis C virus; IDSA = Infectious Diseases Society of America; RAS = resistance-associated substitutions

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Herpes Simplex Virus Disease (Last updated May 26, 2020; last reviewed January 10, 2024)

Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common. Among persons aged 14 to 49 years in the United States, the HSV-1 seroprevalence is 47.8%, and the HSV-2 seroprevalence is 11.9%.[1] While most cases of recurrent genital herpes are due to HSV-2, over the past decade, HSV-1 has become an increasing cause of first-episode genital herpes, causing up to 70% of infections in some populations, such as young adult women and men who have sex with men.[2] Approximately 70% of persons with HIV are HSV-2 seropositive, and 95% are seropositive for either HSV-1 or HSV-2.[3] HSV-2 infection increases the risk of HIV acquisition two- to three-fold,[4,5] and in coinfected patients, HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions.[6]

Clinical Manifestations

Orolabial herpes (commonly known as cold sores or fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations of oral HSV-1 include a sensory prodrome in the affected area, rapidly followed by lesions on lips and oral mucosa that evolve in stages from papule to vesicle, ulcer, and crust. The course of illness in untreated patients is 5 days to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is typically caused by HSV-2 and is the most common manifestation of HSV-2 infection. Increasingly, first-episode genital herpes is caused by HSV-1 and is indistinguishable from HSV-2 infection, although recurrences and viral shedding occur less often with genital HSV-1 infection. Typical genital mucosal or skin lesions evolve through stages of papule, vesicle, ulcer, and crust. Ulcerative lesions are usually the only stage observed on mucosal surfaces, but vesicles are commonly seen on skin on or around the genitals (e.g., the penile shaft, mon pubis, thighs). Local symptoms might include a sensory prodrome consisting of pain and pruritus. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.[7] These classic manifestations occur in some patients, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized. Regardless of the clinical severity of infection, viral shedding on mucosal surfaces occurs frequently and can result in transmission. HSV shedding occurs more frequently in persons with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3 than in those with higher CD4 counts.[8,9] An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but recurrences and viral shedding occur less often with genital HSV-1 infection.

HSV is a significant cause of proctitis in men with HIV infection who have sex with men and may not be associated with external anal ulcers.[10] In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations can occur. These lesions have been reported most often in those with CD4 counts <100 cells/mm^3 and also may be associated with acyclovir-resistant HSV.[11] In addition, atypical presentations such as hypertrophic genital HSV,[12,13] which mimics neoplasia and requires biopsy for diagnosis, may be seen in persons with HIV infection.

The manifestations of non-mucosal HSV infections (e.g., HSV keratitis, HSV encephalitis, HSV hepatitis, herpetic whitlow) are similar to those observed in HIV-seronegative individuals. Disseminated HSV infection is rare, even in profoundly immunosuppressed patients. HSV retinitis manifests as acute retinal necrosis, which can lead rapidly to loss of vision.

Diagnosis

Because mucosal HSV infections cannot be diagnosed accurately by clinical examination, a laboratory diagnosis of all suspected HSV mucosal infections should be pursued.[14] HSV DNA polymerase chain

reaction (PCR), and viral culture are preferred methods for diagnosis of mucocutaneous lesions potentially caused by HSV. PCR is the most sensitive method of diagnosis. HSV detected in genital lesions should be typed as HSV-1 or HSV-2. The frequency of recurrences is greater for HSV-2 than for HSV-1, and therefore knowledge of viral type is helpful for counseling purposes.

Type-specific serologic assays are commercially available and can be used for diagnosis of HSV-2 infection in asymptomatic individuals or those with atypical lesions. Type-specific serologic screening for HSV-2 for persons with HIV infection can be considered. However, providers should be aware that there are some important limitations of currently available serologic tests. In particular, false positive HSV-2 serologic test results occur with the enzyme immunoassay antibody tests, particularly at low index values (1.1–3.5).[15-17] In such situations, confirmatory testing with a second serologic test is recommended in the 2015 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease Treatment Guidelines.[18] A diagnosis of HSV-2 should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2015 CDC Sexually Transmitted Disease Treatment Guidelines.[18] Serologic screening for HSV-1 infection **is not recommended**.

Preventing Exposure

Although most people with HIV also have HSV-1 and HSV-2 infections, it is important to prevent HSV-2 acquisition in those who do not have HSV-2. Persons with HIV who are HSV-2 seronegative should consider asking their partners to be tested using HSV type-specific serology before initiating sexual activity because disclosure of HSV-2 in heterosexual HIV-negative, HSV-2-discordant couples was associated with reduced risk of transmission of HSV-2 **(BII)**.[19] Consistent use of latex condoms reduced HSV-2 acquisition among heterosexual couples, and their use should be encouraged to prevent transmission of HSV-2 and other sexually transmitted pathogens **(AII)**.[20,21]

Sexual transmission of HSV most often occurs during episodes of asymptomatic viral shedding. However, persons with HIV should specifically avoid sexual contact with partners who have overt genital or orolabial herpetic lesions **(AII)**.

In HSV-2 seropositive persons who have symptomatic genital herpes but not HIV, suppressive antiviral therapy (e.g., valacyclovir 500 mg once daily) reduced HSV-2 transmission to susceptible heterosexual partners by 48%.[22] However, in HIV-1/HSV-2-seropositive persons not on antiretroviral therapy (ART), suppressive acyclovir (400 mg twice daily) did not prevent HSV-2 transmission to HSV-2 seronegative partners.[23] Suppressive anti-HSV therapy to prevent HSV-2 transmission to susceptible partners **is not recommended** for persons with HIV/HSV-2 coinfection who are not on ART **(AI)**. There are no data available regarding use of suppressive therapy to prevent genital HSV-1 transmission.

Preventing Disease

Prophylaxis with antiviral drugs to prevent primary HSV infection **is not recommended (AIII)**. In clinical trials, pre-exposure prophylaxis with vaginal tenofovir gel and oral tenofovir disoproxil fumarate (TDF) or with TDF/emtricitabine has been associated with reduced risk of HSV-2 acquisition in persons without HIV.[24-26] However, HSV-2 seronegative persons with HIV on TDF-containing ART regimens are at similar risk of acquiring HSV-2 as those on non-TDF containing ART regimens, suggesting that TDF is not effective in preventing HSV-2 acquisition in persons with HIV infection.[27] The dose, duration, timing, and efficacy of anti-HSV prophylaxis after known or suspected exposure to HSV has not been evaluated. No vaccine for prevention of HSV infection is available. Some studies have shown that medical male circumcision (MMC) decreased the risk of HSV-2 acquisition in African men without HIV,[28,29] and may be associated with decreased risk of HSV-2 transmission to female partners.[30] However, MMC to decrease risk of HSV-2 acquisition and transmission has not been studied among men with HIV and therefore **is not recommended** for the sole purpose of preventing HSV acquisition **(AIII)**.

Treating Disease

Patients with HSV infections can be treated with episodic antiviral therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. Acyclovir, valacyclovir, and famciclovir are effective for suppressive and episodic therapy. Valacyclovir is the prodrug of acyclovir, and has improved oral bioavailability, with decreased dosing frequency, compared to acyclovir. When deciding on suppressive therapy for genital HSV-2 infection in persons with HIV and HSV-2 coinfection, factors to consider include the frequency and severity of HSV recurrences and risk for genital ulcer disease (GUD) when initiating ART.[31] Episodic treatment for individual recurrences of GUD does not influence the natural history of genital HSV-2 infection.

Patients with orolabial HSV lesions can be treated with oral acyclovir, valacyclovir, or famciclovir for 5 days to 10 days **(AIII)**. First episodes of genital HSV should be treated with oral acyclovir, valacyclovir, or famciclovir for 7 days to 10 days; recurrences can be treated for 5 to 10 days **(AI)**. Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir **(AIII)**.[11,32] Once the lesions begin to regress, patients can be switched to oral antiviral therapy. Therapy should be continued until the lesions have completely healed. Although disseminated disease due to HSV is rare in persons with HIV, HSV necrotizing retinitis can occur, which may be difficult to distinguish clinically from retinitis caused by varicella-zoster virus.

Special Considerations with Regard to Starting Antiretroviral Therapy

Orolabial and genital HSV should not influence the decision on when to start ART in persons with HIV. Transient increases in HSV-2–associated genital ulcers have been observed during the first 6 months after initiation of ART in HIV/HSV-2 coinfected persons. In such cases, suppressive anti-HSV therapy can be considered. The frequency and severity of clinical episodes of genital herpes is often reduced in individuals after immune reconstitution on ART. However, immune reconstitution does not reduce the frequency of genital HSV shedding.[33]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed for patients receiving episodic or suppressive HSV therapy unless they have advanced renal impairment. However, for patients receiving high-dose IV acyclovir, monitoring of renal function, and dose adjustment as necessary, are recommended at initiation of treatment and once or twice weekly for the duration of treatment.

HSV-2 shedding and GUD can increase in the first 6 months after initiation of ART, particularly in those with low CD4 counts.[34,35] Mucocutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in individuals initiating ART and have been attributed to immune reconstitution inflammatory syndrome (IRIS).[36]

Managing Treatment Failure

Treatment failure due to acyclovir resistance should be suspected if herpes-related lesions do not begin to resolve within 7 days to 10 days after initiation of anti-HSV therapy. In persons with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing done to confirm drug resistance **(AII)**.[37] Phenotypic testing of viral isolates has been the gold standard method for assessing HSV resistance; genotypic testing is not yet available.

The treatment of choice for acyclovir-resistant HSV is IV foscarnet **(AI)**.[38,39] IV cidofovir is a potential alternative **(CIII)**. A novel agent, the helicase-primase inhibitor pritelivir, is currently being testing in clinical trials for treatment of acyclovir-resistant herpes in immunocompromised persons (*ClinicalTrials. gov* Identifier: NCT03073967). There is an Expanded Access Program available for oral pritelivir in these populations; for more information see AiCuris Pritelivir Early Access website. Topical trifluridine, foscarnet,

cidofovir, and imiquimod also have been used successfully to treat external lesions, although prolonged application for 21 days to 28 days or longer may be required **(CIII)**.[40-44]

Preventing Recurrence

Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences of HSV lesions and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences **(AI)**.[14,45] Suppressive therapy for HSV may be continued indefinitely, without regard to improved CD4 count, although the need for continued therapy should be addressed on an annual basis, particularly if immune reconstitution has occurred **(BIII)**. Persons starting ART with CD4 counts <250 cells/mm^3 have an increased risk of HSV-2 shedding and GUD in the first 6 months on ART. Suppressive acyclovir decreases the risk of GUD nearly 60%, and may be recommended for persons with CD4 counts <250 cells/mm^3 starting ART **(BI)**.

In persons with HIV not on ART, suppressive anti-HSV therapy also results in a decrease in HIV RNA levels in plasma, anal, and genital secretions, and in a lower risk of HIV progression.[46] However, antiviral regimens for herpes do not decrease the risk of HIV transmission to sexual partners, and should not be used in place of ART to delay HIV progression.[47] In persons who are taking ART, suppressive HSV antivirals do not delay HIV progression, improve CD4 recovery, or decrease markers of systemic inflammation[48,49] and are not useful for these ends **(AI)**.

Although there is no data specific to persons with HIV, in hematopoietic stem cell recipients, the risk of developing acyclovir-resistant HSV was lower with daily suppressive acyclovir therapy than with episodic therapy.[50]

Special Considerations During Pregnancy

Laboratory testing to diagnose mucocutaneous HSV infections is the same for pregnant women as for non-pregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy. Visceral disease following HSV acquisition is more likely to occur during pregnancy and can be fatal. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe, particularly during the second and third trimesters **(AIII)**.[51] One recent case–control study suggested a higher risk of gastroschisis associated with both genital herpes and acyclovir use during the first trimester of pregnancy.[52] The use of valacyclovir and famciclovir during pregnancy has been described, and the antiviral drugs also appear to be safe and well tolerated during the third trimester.[53] Given its simplified dosing schedule valacyclovir is an option for treatment and suppressive therapy during pregnancy **(CIII)**.

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate. The rate of neonatal HSV transmission in HSV-2-seropositive pregnant women is low, except in those who acquire genital HSV infection late in pregnancy. However, when HSV transmission does occur, the adverse sequelae for the neonate can be very significant. The predominant risk for neonatal HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor **(BII)**.[14] Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes outbreaks and reduces the need for cesarean delivery for recurrent HSV in HIV-seronegative women[54] and is likely to have similar efficacy in women with HIV infection. However, neonatal HSV disease has been reported in infants born to women treated with antenatal suppressive antiviral therapy.[55] Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks' gestation for pregnant women with recurrences of genital herpes during pregnancy **(BII)**.[56] Suppressive therapy for women who are seropositive for HSV-2 but no history of genital lesions **is not recommended**. Maternal genital herpes was a risk factor for perinatal HIV transmission in the era preceding availability of ART.[57] Whether HSV facilitates HIV transmission in pregnant women on ART is unknown.

Recommendations for Treating Herpes Simplex Virus Infections

Note: Compared to acyclovir, valacyclovir has improved bioavailability and requires less frequent dosing.

Treating Orolabial Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day **(AIII)**, *or*
- Famciclovir 500 mg PO twice a day **(AIII)**, *or*
- Acyclovir 400 mg PO three times a day **(AIII)**

Treating Initial Genital Lesions (Duration: 7–10 Days) or Recurrent Genital Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day **(AI)**, *or*
- Famciclovir 500 mg PO twice a day **(AI)**, *or*
- Acyclovir 400 mg PO three times a day **(AI)**

Treating Severe Mucocutaneous HSV Infections (AIII)

- For initial therapy, acyclovir 5 mg/kg IV every 8 hours
- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

Chronic Suppressive Therapy

Indications:

- For patients with severe recurrences **(AI)**, *or*
- Patients who want to minimize the frequency of recurrences **(AI)**, including pregnant women, *or*
- To reduce the risk of genital ulcer disease in patients with CD4 counts <250 cells/mm^3 who are starting ART **(BI)**

Treatment:

- Valacyclovir 500 mg PO twice a day **(AI)**, *or*
- Famciclovir 500 mg PO twice a day **(AI)**, *or*
- Acyclovir 400 mg PO twice a day **(AI)**
- Evaluate ongoing need for suppressive therapy annually.

For Acyclovir-Resistant Mucocutaneous HSV Infections

Preferred Therapy:

- IV Foscarnet 80–120 mg/kg/day in 2–3 divided doses until clinical response **(AI)**

Alternative Therapy (Duration: ≥21–28 Days, Based on Clinical Response) **(CIII)**:

- IV cidofovir 5 mg/kg once weekly, *or*
- Topical trifluridine 1% three times a day, *or*
- Topical cidofovir 1% gel once daily, *or*
- Topical imiquimod 5% cream three times a week, *or*
- Topical foscarnet 1% five times a day

Notes:

- Topical formulations of trifluridine, cidofovir, and foscarnet are not commercially available.
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir and foscarnet.
- An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir-resistant HSV infection; for more information see AiCuris Pritelivir Early Access website.

Key: ART = antiretroviral therapy; HSV = herpes simplex virus; IV = intravenously; PO = orally

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Histoplasmosis

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Epidemiology

Histoplasmosis is a fungal infection caused by the dimorphic fungus *Histoplasma capsulatum (H. capsulatum)*. The fungal infection is endemic to the central and south-central United States, where it is especially common in the Ohio and Mississippi River valleys. Microfoci of infection exist elsewhere in the eastern United States. Histoplasmosis is also found in Latin America and the Caribbean, Asia, and Africa. In some Latin American countries, histoplasmosis is one of the most common opportunistic infections in people with HIV, even during the era of highly active antiretroviral therapy (ART).[1-3] A CD4 T lymphocyte (CD4) cell count <150 cells/mm^3 is associated with an increased risk of symptomatic illness in people with HIV.[4,5] The risk for and incidence of symptomatic disease is generally higher at lower CD4 counts in people with HIV, but disease can present with counts as high as 350 cells/mm^3.

Histoplasmosis is acquired by the inhalation of microconidia that form in the mycelial phase of the fungus in the environment. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. Diminished cellular immunity can lead to a reactivation of a quiescent focal infection acquired years earlier; this is the presumed mechanism for disease occurrence in nonendemic areas.

Clinical Manifestations

There is a spectrum of disease from asymptomatic and self-limited pulmonary disease to disseminated disease in those with low CD4 counts (≤200 cells/mm^3). In people with advanced HIV, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough and dyspnea occur in approximately 50% of patients.[4,6] Gastrointestinal (GI) disease usually manifests as fever, nausea and vomiting, diarrhea, abdominal pain, and weight loss.[7] In a case series of people with HIV in Panama, diarrhea with or without fever was seen in 50% of the patients with histoplasmosis,[8] and in another series from French Guiana, GI symptoms occurred in 70% of patients with histoplasmosis.[3] Central nervous system (CNS) and cutaneous manifestations occur in no more than 20% of patients. People with CNS histoplasmosis typically experience fever and headache; if brain involvement is present, they may also experience seizures, focal neurological deficits, septic meningitis, or changes in mental status.[4] Approximately 10% of patients with low CD4 counts experience septic shock, multiorgan failure, and/or pericardial effusion and pericarditis requiring rapid therapy.[4] In such cases, blood cultures and *Histoplasma* antigen tests of serum and urine are helpful diagnostically.[4,9] In patients with CD4 counts >200 cells/mm^3, histoplasmosis is often limited to the respiratory tract, and they may present with cough, pleuritic chest pain, and/or fever.[9]

Diagnosis

The detection of *Histoplasma* antigen in blood or urine (the detection method preferred by the World Health Organization) is a sensitive method for the rapid diagnosis of disseminated histoplasmosis in people with HIV.[10] This test should be obtained for any person with HIV and low CD4 counts who

has the above-mentioned symptoms and who lives, or has previously lived, in an area in which *H. capsulatum* is commonly found.

In a study using a certain quantitative enzyme immunoassay (EIA), *Histoplasma* antigen was detected in 100% of urine samples and 92% of serum samples from people with AIDS and disseminated histoplasmosis.[11] Another EIA employs a monoclonal antibody to detect *Histoplasma* galactomannan and has been reported to have a sensitivity of 91% and a specificity of 91%.[12] A lateral flow assay for the detection of *Histoplasma* antigen in urine was reported to have a sensitivity of 96% and specificity of 96%.[13] Antigen detection in bronchoalveolar lavage fluid may also be a useful method for the diagnosis of pulmonary histoplasmosis.[14]

In people with severe disseminated histoplasmosis, peripheral blood smears might occasionally show the organisms engulfed by white blood cells if observed with careful attention. Histopathological examination of biopsy material from involved tissues often demonstrates small yeast cells 2 to 4 µm in diameter, which are characteristic of histoplasmosis.

In >85% of people with HIV and disseminated histoplasmosis, *H. capsulatum* can be cultured from blood (using the lysis-centrifugation technique), bone marrow, respiratory secretions, or samples from other involved sites; however, the organism requires several weeks to grow before final results can be interpreted.[15] Serologic tests for antibodies are less useful than antigen assays for people with HIV and disseminated histoplasmosis but may be helpful for those with pulmonary disease and reasonably intact immune responses.[15,16]

The diagnosis of *Histoplasma* meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.[17] In a review of CNS histoplasmosis that included people with HIV, cultures were positive in 38% of study participants.[18] *Histoplasma* antigen can be detected in CSF in a far greater number of cases, and antibodies against *H. capsulatum* are seen in at least one-half of cases.[18] A positive antigen or antibody test result from CSF is diagnostic for histoplasmosis. In cases in which none of these specific tests are positive, a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not attributable to another cause.

Preventing Exposure

People with HIV who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to *H. capsulatum*, but those with CD4 counts <200 cells/mm^3 should be counseled to minimize exposure to activities associated with an increased risk for histoplasmosis **(BIII).** These activities include creating dust when working with surface soil; cleaning chicken coops; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing buildings; and exploring caves.[19]

Preventing Disease

Preventing the First Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)
Indications for Initiating Primary Prophylaxis (BI)
• People with CD4 count <150 cells/mm³ and who are at high risk because of occupational histoplasmosis exposure *or* who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 person-years)
Preferred Therapy
• Itraconazole 200 mg PO once daily **(BI)**
Criteria for Discontinuing Primary Prophylaxis (BIII)
• Stable ART, *and*
• CD4 count ≥150 cells/mm³ for 6 months, *and*
• Undetectable HIV-1 viral load
Indication for Restarting Primary Prophylaxis
• CD4 count <150 cells/mm³ **(BIII)**

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the incidence of histoplasmosis, although not mortality, in people who have advanced HIV (CD4 counts <150 cells/mm³) and live in areas where histoplasmosis is highly endemic.[20] Based on these data, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) continues to recommend itraconazole at a dose of 200 mg daily as primary prophylaxis **(BI)** to people with CD4 counts <150 cells/mm³ who are at high risk because of occupational histoplasmosis exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 person-years) **(BI).** However, as with other opportunistic infections in the current era of more effective ART, it may be reasonable to consider withholding primary prophylaxis if ART can be immediately initiated and there is an accompanying rise in CD4 cell count above the threshold of risk **(CIII).** Fluconazole has yet to show activity in a prophylaxis setting for histoplasmosis. The role of screening for *Histoplasma* antigen to define people at risk for developing infection has not been studied.

If used, primary prophylaxis should be discontinued in people on ART once CD4 counts are ≥150 cells/mm³ for 6 months and HIV-1 viral loads are undetectable **(BIII).** Prophylaxis should be restarted if the CD4 count falls to <150 cells/mm³ **(BIII).**

Treating Disease

Treating *Histoplasma capsulatum* Infections
Treating Severe Disseminated Disease
Induction Therapy (≥2 Weeks or Until Clinically Improved)
Preferred Therapy
• Liposomal amphotericin B 3 mg/kg IV daily **(AI)**

Alternative Therapy

- Amphotericin B lipid complex 5 mg/kg IV daily **(AIII)**

Maintenance Therapy (≥12 Months)

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day **(AII)**

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole and only moderately ill.

- Posaconazole 300 mg extended-release tablet PO twice daily for 1 day, then 300 mg PO once daily **(BIII)**, *or*

- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily **(BIII)**, *or*

- Fluconazole 800 mg PO once daily **(CII)**

Treating Mild-to-Moderate Disseminated Disease or Acute Pulmonary Histoplasmosis in People With CD4 <300 cells/mm^3

Induction and Maintenance Therapy (≥12 Months)

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day **(AII)**

Alternative Therapy

- Posaconazole 300 mg extended-release tablet PO twice daily for 1 day, then 300 mg PO once daily **(BIII)**, *or*

- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily **(BIII)**, *or*

- Fluconazole 800 mg PO once daily **(CII)**

Treating Histoplasma Meningitis

Induction Therapy (4–6 Weeks Depending on Symptom Resolution and Improvement of CSF Findings)

Preferred Therapy

- Liposomal amphotericin B 5 mg/kg IV daily **(AIII)**

Alternative Therapy

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(BIII)**

Maintenance Therapy (≥12 Months and Until Resolution of Abnormal CSF Findings)

Preferred Therapy

- Itraconazole 200 mg PO two or three times a day **(AIII)**

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole and only moderately ill.

- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily **(BIII)**, *or*

- Fluconazole 800 mg PO once daily **(CII)**—for people who cannot tolerate both itraconazole and voriconazole

Long-Term Suppressive Therapy

Indications

- Severe disseminated or CNS infection after completing maintenance therapy for ≥12 months of treatment **(AIII)**, *or*

- Relapse despite appropriate initial therapy (after reinduction therapy) **(BIII)**

Preferred Therapy

- Itraconazole 200 mg PO once daily **(AIII)**

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole.

- Fluconazole 400 mg PO once daily **(CII)**, *or*

- Voriconazole 200 mg PO twice daily **(BIII)**, *or*

- Posaconazole 300 mg PO daily **(BIII)**

Criteria for Discontinuing Long-Term Suppressive Therapy (AII)

- Receipt of azole treatment for >1 year, *and*

- Negative fungal blood cultures, *and*

- Serum or urine *Histoplasma* antigen below the level of quantification, *and*

- Undetectable HIV viral load on stable ART, *and*

- CD4 count ≥150 cells/mm^3 and on ART for ≥6 months

Indication for Restarting Long-Term Suppressive Therapy

- CD4 count <150 cells/mm^3 **(BIII)**

Other Considerations

- Random itraconazole serum concentrations should be measured in all patients after 2 weeks of therapy (the time it usually takes to reach a steady state) to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions **(AIII)**.

- Random serum concentrations (itraconazole plus hydroxyitraconazole) should be between 1 and 2 µg/mL. Concentrations ≥5 µg/mL are associated with an increased frequency and severity of adverse effects.

- Oral itraconazole liquid solution is preferred over the capsule formulation because of improved absorption but is less well tolerated. However, it is not necessary to use the liquid solution if random serum itraconazole concentration is ≥1.0 µg/mL with the capsule formulation **(AIII)**.

- Trough voriconazole serum concentrations should be measured after 5 days of therapy (the time it usually takes to reach a steady state) with the goal of achieving a concentration of 1 to 5 µg/mL. Concentrations are highly variable among patients, and for individual patients, concentrations can vary because of drug–drug interactions. Neurotoxicity and hepatotoxicity are associated with serum concentrations >5 µg/mL, but some patients can experience adverse effects with lower serum concentrations **(AIII)**.

- Trough posaconazole serum concentrations should be measured after 5 days of therapy (the time it usually takes to reach a steady state) to ensure adequate absorption, with a goal of achieving a concentration >1 µg/mL **(AIII)**.

- Acute pulmonary histoplasmosis in patients with HIV and CD4 count ≥300 cells/mm^3 should be managed the same as in immunocompetent patients **(AIII)**.

- All triazole antifungals have the potential to interact with certain ART agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Drug–Drug Interactions section in the Adult and Adolescent Antiretroviral Guidelines lists these interactions and recommends dose adjustments where feasible. The University of Liverpool HIV Drug Interactions Database provides more detailed information on interactions.

Pregnancy Considerations

- Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis in pregnant patients, especially during the first trimester **(AIII)**.

- In the second and third trimester of pregnancy, itraconazole can be considered if the benefit outweighs the potential risk **(CIII)**.

- Azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**.

- Use of fluconazole, voriconazole, and posaconazole **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system, CSF = cerebrospinal fluid; IV = intravenous; PO = orally

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) induced a more rapid and complete response, lowered mortality rates, and reduced toxicity more efficaciously than standard IV amphotericin B deoxycholate (0.7 mg/kg daily) for the treatment of histoplasmosis associated with AIDS.[21] Based on these findings, patients with symptomatic severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for ≥2 weeks or until they clinically improve **(AI).** IV amphotericin B lipid complex (5 mg/kg daily) can be used if cost is a concern, or if the patient cannot tolerate liposomal amphotericin B **(AIII).**

Step-down therapy to oral itraconazole, 200 mg three times a day for 3 days followed by 200 mg two times a day, should be given for ≥12 months **(AII).**[22] Because absorption of itraconazole can be erratic and because of potential drug interactions between itraconazole and protease inhibitors, efavirenz, rilpivirine, etravirine, and many other drugs that are cytochrome P450 3A4 (CYP3A4) inducers or inhibitors, random serum concentration of itraconazole should be measured 2 weeks after the start of therapy (see The University of Liverpool HIV Drug Interactions Database) **(AIII).** Combined serum itraconazole and hydroxyitraconazole concentrations should be 1 to 2 μg/mL. Adverse events become more frequent and severe as concentrations increase, with a 26% increase observed when concentrations exceed 5 μg/mL.[23] Itraconazole is a moderately strong CPY3A4 inhibitor, so ART effectiveness also must be considered.

In patients with mild-to-moderate disseminated histoplasmosis, oral itraconazole, 200 mg three times daily for 3 days followed by 200 mg twice daily for ≥12 months, is an appropriate initial therapy **(AII).**[22,24] The liquid formulation of itraconazole, which should be given on an empty stomach, is preferable because it is better absorbed and does not require gastric acid for absorption **(AIII).** However, the capsule formulation of itraconazole is better tolerated than the liquid formulation. If a serum random itraconazole concentration of 1.0 to 2.0 μg/mL has been achieved with the capsule formulation, it is not necessary to use the liquid solution. The capsule formulation should be given with food and cannot be used when the patient requires gastric acid–inhibiting drugs. A formulation of itraconazole, SUBA-itraconazole, has improved absorption and is most likely of all formulations to achieve random itraconazole level (≥1.0 μg/mL).[25] Although this agent likely will prove useful in treating histoplasmosis, SUBA-itraconazole cannot be routinely recommended due to cost and the need for further clinical data on its use for this purpose .

Acute pulmonary histoplasmosis in a person with HIV who has a CD4 count ≥300 cells/mm^3 should be managed the same way as acute pulmonary histoplasmosis in an immunocompetent person (**AIII**).[22] For acute pulmonary histoplasmosis in a person with HIV who has a CD4 count <300 cells/mm^3, the patient should receive therapy similar to that of mild-to-moderate disseminated disease (**AIII**).

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dose of 5 mg/kg IV daily for 4 to 6 weeks depending on the resolution of symptoms and improvement of abnormal CSF findings (**AIII**). Amphotericin B deoxycholate 0.7 to 1.0 mg/kg IV daily can be used as an alternative if liposomal amphotericin B is not available (**BIII**). A reduction in *Histoplasma* antigen is encouraging. This initial IV therapy with amphotericin B should be followed by maintenance therapy with oral itraconazole at a dose of 200 mg two or three times daily for ≥12 months with dose adjustment based on interactions with ART and itraconazole serum concentration until abnormal CSF findings are resolved (**AIII**).[22] Voriconazole is an alternative to itraconazole for *Histoplasma* meningitis (**BIII**). The Panel recommends fluconazole 800 mg daily as an alternative maintenance therapy for those who are intolerant of itraconazole and voriconazole (**CII**).[26]

Oral posaconazole and voriconazole have been reported to be effective in treating histoplasmosis in a small number of people with HIV or other immunosuppressive conditions[27-30] and are therefore recommended as alternatives for those who are only moderately ill and intolerant of itraconazole (**BIII**). Oral voriconazole should be administered at a dose of 400 mg two times a day for 1 day, then 200 mg two times a day (**BIII**). If voriconazole is used, trough serum concentrations should be measured after 5 days of therapy, with a goal of achieving a serum concentration of l to 5 µg/mL (**AIII**). Concentrations are highly variable among different people and over time within a given person and may vary because of absorption issues and drug–drug interactions (see The University of Liverpool HIV Drug Interactions Database). Neurotoxicity and hepatotoxicity are associated with serum concentrations >5 µg/mL, but individual patients can experience adverse effects, such as hepatitis and neurotoxicity, even with lower serum concentrations. Oral posaconazole should be administered at a dose of 300 mg of extended-release tablets twice daily for 1 day, then 300 mg once daily (**BIII**). Posaconazole serum concentrations should be measured after 5 days of therapy to ensure adequate absorption, with a goal of achieving a concentration of >1 µg/mL (**AIII**).

Fluconazole is less effective than itraconazole for the treatment of histoplasmosis but has been shown to be moderately effective at a dose of 800 mg daily (**CII**).[26] Isavuconazole has been used in too few patients with histoplasmosis to be routinely recommended at this time but might be considered when other triazoles such as itraconazole, voriconazole, and posaconazole cannot be used. The echinocandins do not have activity against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis (**AIII**).

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining a response to therapy. Antigen titers should be checked monthly for the first 3 months and then every 3–4 months, until negative. Blood titers will drop faster than urine titers, and titers will drop faster with polyene treatment compared to azole treatment.[31] A significant rise in antigen level suggests relapse and consideration for treatment changes.

People with HIV diagnosed with histoplasmosis should start ART as soon as possible after initiating antifungal therapy **(AIII).** Life-threatening immune reconstitution inflammatory syndrome (IRIS) has been uncommonly reported in people with HIV who have histoplasmosis.[32,33] Therefore, ART should not be withheld because of concern for the possible development of IRIS **(AIII).**[34]

All triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents and other anti-infective agents. Refer to Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections and the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for a list of interactions and recommendations for dose adjustments, where feasible. Itraconazole has caused worsening heart failure, adrenal insufficiency, and transaminitis. Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections provides a list of antifungal adverse reactions.

Managing Treatment Failure

Liposomal amphotericin B should be used in patients who are severely ill or who have failed to respond to initial azole antifungal therapy **(AIII).** Oral posaconazole and oral voriconazole are recommended as reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII);**[27-30] fluconazole at a dose of 800 mg daily also can be used **(CII).**[26] Drug interactions may limit the use of voriconazole in patients who are taking certain non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, etravirine) or protease inhibitors. Posaconazole has fewer known drug interactions with ART medications than voriconazole.

Prevention of Relapse

Long-term suppressive therapy with oral itraconazole (200 mg daily) should be administered to people with severe disseminated infection or CNS infection for ≥12 months after completing induction therapy **(AIII)** or after reinduction therapy to those whose disease relapsed despite initial receipt of an appropriate therapy **(BIII).**[35,36] Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily **(CII).**[26,37] Although the role of voriconazole or posaconazole has not been evaluated in sufficiently powered studies, they may be reasonable options for patients who received these drugs as maintenance therapy **(BIII).** Long-term therapy is started after symptoms have abated and antigen titer is decreasing.

A study sponsored by the AIDS Clinical Trials Group (ACTG) reported that it was safe to discontinue itraconazole treatment for histoplasmosis in people who had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum or urine antigen <4.1 units, and a CD4 count >150 cells/mm^3; and had been on ART for 6 months.[35] No relapses were evident among 32 study participants who were followed for a median of 24 months. Thus, it appears safe to discontinue suppressive azole antifungal therapy in patients who have a serum or urine antigen below the limit of quantification in ng/mL, with CD4 count ≥150 cells/mm^3, on ART for 6 months, and who have an undetectable HIV viral load **(AII).** Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm^3 **(BIII).**[35]

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis in pregnant patients, especially during the first trimester **(AIII).** Extensive clinical

experience with amphotericin B has not documented teratogenicity. Because amphotericin B crosses the placenta, infants born to those treated with amphotericin B should be evaluated for adverse effects, including renal dysfunction and hypokalemia.[38]

Although the safety of amphotericin B in pregnancy is well established, less is known about itraconazole. The drug is known to be embryotoxic and teratogenic in rodents. Teratogenic effects included major skeletal defects, encephaloceles, and macroglossia. Because of this, the manufacturer recommends that people of childbearing potential use contraceptives during and for 2 months after treatment.[39] Interestingly, prospective cohort studies of more than 200 women with first trimester itraconazole exposure did not show an increased risk of congenital malformation, but these studies reported uncontrolled doses and durations and have low power to detect differences.[40,41] In the second and third trimester of pregnancy, itraconazole can be considered if the benefit outweighs the potential risk **(CIII).**[40,41] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII).**[42] Although several cohort studies and a systematic review have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short-term exposure to fluconazole.[43-45] Reports of increased birth defects associated with fluconazole use include data from the Quebec Pregnancy Cohort, a population-based cohort with a prospective data collection on all pregnancies covered by Quebec Prescription Drug Insurance from 1998 to 2015, which demonstrated an association between higher fluconazole exposures (>150 mg dosing) during the first trimester and cardiac septal closure defects.[46] In addition, five cases of fluconazole embryopathy—a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures—have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.[47-50] Additionally, fluconazole use in the first trimester has been associated with an increased risk of spontaneous abortion and stillbirth.[51] Data derived from the Quebec Pregnancy Cohort supported an increased risk of spontaneous loss with fluconazole use at low doses but found no association with risk of stillbirth.[46] A recent analysis of registry data from Sweden and Norway did not find an increase in stillbirth or neonatal death associated with exposure to fluconazole at any dose during pregnancy.[52]

In animals, voriconazole (at doses lower than recommended human doses) and posaconazole are teratogenic and embryotoxic. No adequately controlled studies have been conducted of these drugs in humans. Use of fluconazole, voriconazole, and posaconazole **should be avoided** in pregnancy, especially in the first trimester **(AIII).**

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Human Herpesvirus-8 Disease

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Epidemiology

The seroprevalence of human herpesvirus-8 (HHV-8)—also known as Kaposi sarcoma-associated herpesvirus (KSHV)—varies worldwide and is estimated to be 1% to 5% in the general U.S. population[1,2] compared with 10% to 20% in certain Mediterranean countries and 30% to 80% in parts of sub-Saharan Africa.[3] In the United States, men who have sex with men (MSM) and persons with HIV infection are at increased risk for HHV-8 infection. Among MSM without HIV infection, the seroprevalence ranges from 13% to 20% and HHV-8 seroprevalence increases to 30% to 35% among MSM with HIV infection.[4-6] Injection drug use may also be a risk factor for HHV-8 seropositivity,[7] although this association has not been consistently observed.[8]

HHV-8 is etiologically associated with all forms of Kaposi sarcoma (KS) including classic, endemic, transplant-related, and AIDS-related, as well as rare neoplastic disorders (primary effusion lymphoma [PEL] and solid organ variants) and the lymphoproliferative disorder known as multicentric Castleman's disease (MCD). Although the precise pathogenesis for these tumors remains unclear, infection with HHV-8 precedes their development.[9] Patients who are HHV-8 seropositive and exhibit HHV-8 viremia are at increased risk (approximately nine-fold) for developing KS relative to those without HHV-8 viremia.[10] HHV-8 viremia typically accompanies symptomatic episodes of multicentric Castleman's disease.[11]

The overall prevalence of KS in the U.S. was as high as 30% among patients with AIDS prior to the advent of effective antiretroviral therapy (ART).[12] The incidence of KS rose steeply in the United States between 1981 and 1987 and subsequently gradually declined.[13] Reasons for this reduction in KS incidence prior to the widespread availability of ART include the deaths of patients with advanced AIDS who were most susceptible to KS, and the increasing use by individuals with HIV individuals of antiviral drugs that may have had activity against HHV-8 (zidovudine for the treatment of HIV; ganciclovir, foscarnet, and cidofovir use for treatment of CMV disease).[14] Supporting the latter hypothesis, observational studies indicate that patients receiving ganciclovir or foscarnet (but not acyclovir) develop KS at a reduced rate.[15-18] A more marked reduction in KS incidence occurred beginning in 1996, shortly after the introduction of protease inhibitor-containing ART in the U.S. Despite these declines, KS is among the most common cancers among the AIDS population in the U.S.,[19] and HIV infection increases the risk of KS several thousand fold even in the ART era.[20] Notably, KS is a common cancer in many countries in sub-Saharan Africa,[21] fueled in part by the HIV pandemic, and incidence has not declined in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.[22,23] PEL and MCD remain rare relative to KS.[24,25]

KS and PEL are described most frequently among individuals with HIV exhibiting advanced immunosuppression (CD4 T lymphocyte [CD4] cell counts <200 cells/mm^3), although they may occur at any CD4 cell count. Recent reports of KS occurring at higher CD4 cell counts in the United States[26,27] suggest that clinicians caring for patients with HIV should be vigilant for the clinical manifestations of KS in patients at risk of HHV-8 infection, regardless of CD4 cell count. MCD may arise at any CD4 cell count.

Clinical Manifestations

Most individuals latently infected with HHV-8 are asymptomatic.[28] Immunocompetent children and organ transplant recipients infected with HHV-8 may develop a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.[29,30] KS manifestations vary

widely, but most patients have nontender, hyperpigmented, macular or nodular skin lesions. Oral lesions occur in approximately one-third of patients[31] and are predictors of pulmonary involvement and less favorable treatment outcomes.[32-34] Lymphatic involvement is also common and may lead to debilitating lower extremity edema. Involvement of internal viscera occurs in up to 50% of cases and may be difficult to diagnose. Patients with visceral involvement may be asymptomatic, or manifest with shortness of breath, painless rectal bleeding or melena, and other non-specific pulmonary and gastrointestinal symptoms.[35-40]

PEL characteristically presents with effusions isolated within the pleural, pericardial, or abdominal cavities,[41] but mass lesions and "extracavitary" disease within skin, hematopoietic organs, and the gastrointestinal tract have been described.[42-44] MCD routinely manifests with systemic symptoms including fever and night sweats, and findings on examination including generalized adenopathy, fever and hepatosplenomegaly.[24,45] MCD may mimic other inflammatory conditions including sepsis, with hypotension, clinical evidence of a systemic inflammatory response, and progression to multi-organ failure.[24,46,47]

Another HHV-8- associated condition, the KSHV inflammatory cytokine syndrome (KICS), has been more recently described.[48-50] Patients with this syndrome display MCD-like inflammatory symptoms, but do not have pathological findings of MCD. Patients with KICS are frequently critically ill and demonstrate marked elevations in IL-6 and IL-10, as well as high plasma HHV-8 viral loads. KICS may contribute to the inflammatory symptoms seen in some patients with severe KS or PEL, and there may be significant clinical overlap between these conditions.

Diagnosis

The diagnoses of KS, MCD and PEL depend on cytologic and immunologic cell markers, as well as histology. Clinical diagnosis alone is not sufficient for KS, and tissue examination is needed to confirm the diagnosis.[51,52] Confirmation of these diagnoses is achieved through immunohistochemical staining of tumors with antibodies recognizing the HHV-8-encoded latency-associated nuclear antigen (LANA).[53,54] While not commercially available, diagnoses may also be confirmed utilizing polymerase chain reaction (PCR) to identify HHV-8 DNA within tumor tissue.[53,54] Use of serologic testing for HHV-8 antibodies is currently not indicated for either diagnostic testing or routine screening for HHV-8-related illnesses due to lack of standardization and poor sensitivity and specificity of these assays.[55] In addition, use of PCR to quantify HHV-8 in the peripheral blood has no established role in the diagnosis of KS, MCD, or PEL.[11]

HHV-8 Transmission/Preventing Exposure

The mode(s) of transmission of HHV-8 remains unclear, but epidemiologic and virologic data suggest that saliva is a source of infectious virus and may be an important route of transmission. Asymptomatic HHV-8 infection is often associated with HHV-8 shedding in the saliva and occasional shedding in genital secretions.[4,28,56] In a study of 50 HHV-8-infected MSM in the U.S., HHV-8 was detected by PCR in the saliva of 39% of participants and on more than 35% of days on which samples were obtained.[4] HHV-8 shedding is also common among persons in sub-Saharan Africa. Among HHV-8-infected adults without KS in Uganda, 22% had HHV-8 DNA detected in saliva and 3% in genital secretions; HHV-8 was also detected in saliva of 68% of commercial sex workers in Kenya.[57,58] Based on these observations, viral shedding may result in HHV-8 transmission to uninfected partners through behaviors associated with exposure to saliva or genital secretions. HHV-8 transmission through blood transfusion has been reported in Uganda, where HHV-8 is endemic;[59] however, studies from the U.S. and Western Europe have not found evidence to support HHV-8 transmission through blood transfusion.[60,61]

Recommendations to prevent exposure to HHV-8 do not yet exist; screening patients for HHV-8 serostatus or behavioral modifications to limit potential exposures have not been validated and are not currently recommended.

Preventing Disease

Despite observational evidence supporting a role for anti-HHV-8 therapy in preventing the development of KS, the toxicity of current anti-HHV-8 treatments outweighs the potential use for prophylaxis (**AIII**). Because strong risk factors for the development of KS in HIV-positive individuals include both low CD4-positive T cell count[62] and uncontrolled viremia,[63] early initiation of ART is likely to be the most effective measure for the prevention of KS (**AII**). Although epidemiologic data are somewhat conflicting, there are no antiretroviral agents which have proven clearly superior for the prevention of KS.[60-65] Therefore, specific classes of ART for prevention of KS or other HHV-8-associated illnesses are not recommended (**AII**).

Treating Disease

KS: Chemotherapy, in combination with ART, should be administered to patients with visceral involvement (**AI**) and is likely to be a useful adjunctive therapy in individuals with disseminated cutaneous KS (**BIII**).[64-67] Liposomal doxorubicin and paclitaxel exhibit comparable response rates and progression-free survival, although liposomal doxorubicin exhibits less high-grade toxicity relative to paclitaxel and is, therefore, generally preferred as first-line therapy (**AI**).[64] Paclitaxel has proven effective with relapse following treatment failure with liposomal doxorubicin.[67] Importantly, concurrent use of corticosteroids in patients with KS should be either avoided or used with caution and under close observation, given the potential for exacerbation of life-threatening disease, as well as an association between the use of corticosteroids and development of KS (**AIII**).[68-70] KS arising in the setting of organ transplantation is related to the use of corticosteroids and other non-targeted immunosuppressives, especially in geographic areas of high HHV-8 seroprevalence.[71] Transplant-associated KS may be effectively treated or avoided with use of immunosuppressive regimens which include drugs that inhibit the mammalian target of rapamycin (mTOR) such as rapamycin and sirolimus.[71-73]

The antiviral agents ganciclovir, foscarnet, and cidofovir exhibit *in vitro* activity against HHV-8.[74,75] Available data indicate that antivirals have limited efficacy for the treatment of KS (ganciclovir and cidofovir)[76,77] and HHV-8-associated hemophagocytosis (foscarnet).[78,79] Therefore, antiviral agents with activity against HHV-8 are not recommended for KS treatment (**AII**).

PEL: Chemotherapy, in combination with ART, should be administered to patients with PEL (**AIII**), although, given its rarity, there are limited data available from longitudinal observational series or prospective randomized clinical trials. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in combination with ART has demonstrated some benefit, albeit still limited, for PEL, and the combination of infusional etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) demonstrated superior survival relative to CHOP in one pooled analysis (**BII**).[80,81] Rituximab may be considered for rare CD20-positive cases of PEL (**CIII**), and dose-adjusted EPOCH (DA-EPOCH) may be beneficial for some patients (**CIII**).[82,83] Antiviral agents, including valganciclovir or zidovudine, may also be used as adjunctive therapies, but available data are limited for this approach and additive toxicities may limit their utility (**CIII**).[84-86]

MCD: There are no standardized treatments for MCD, but several treatment regimens have been utilized. The use of either IV ganciclovir or oral valganciclovir are options for treatment of MCD (**CII**). A 3-week course of twice-daily IV ganciclovir or oral valganciclovir was associated with remissions in MCD in one report,[87] and a combination of valganciclovir and high-dose zidovudine has led to durable clinical remissions (**CII**).[88]

Rituximab has also emerged as an important adjunctive treatment for MCD **(CII)**,[89,90] although up to one-third of patients receiving rituximab may have subsequent exacerbations or emergence of KS.[91,92] For patients with concurrent diagnoses of KS and MCD, use of both rituximab and liposomal doxorubicin is recommended **(BII)**.[45] Therapeutic monoclonal antibodies targeting either interleukin-6 (IL-6) or the IL-6 receptor have also proven effective for some patients with MCD and may be utilized in some situations **(BII)**.[93-95] At this time, there is insufficient evidence to recommend monitoring IL-6 levels for diagnostic or prognostic purposes. Although corticosteroids are potentially effective as an adjunctive therapy for MCD, they should be used with caution or avoided, especially in patients with concurrent KS, given potential for exacerbation of life-threatening KS **(AIII)**.[68-70]

Detailed recommendations for the treatment of HHV-8 malignancies (including chemotherapy and radiation therapy) are beyond the scope of these guidelines. Treatment should be undertaken in consultation with an experienced specialist with appropriate guidance from both oncology and infectious disease specialists **(AIII)**. Preferred ART to be given concurrently with chemotherapy for HHV-8 malignancies should be chosen to minimize drug-drug interactions and additive toxicities.

Special Considerations When Starting Antiretroviral Therapy

Early initiation of ART may prevent incident KS and PEL.[74,96] ART that suppresses HIV replication should be administered to all patients with HIV and KS **(AII)**, PEL **(AIII)**, or MCD **(AIII)**, although insufficient evidence exists to support using one ART regimen over another.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Immune reconstitution inflammatory syndrome (IRIS) may occur among HHV-8-infected patients initiating ART.

KS: KS-IRIS is characterized by either first presentation of KS ("unmasking"), or paradoxical worsening of pre-existing KS following ART initiation, and can be associated with significant morbidity and mortality.[97] Studies in the U.S. and Europe reveal that KS is the most commonly reported form of IRIS, occurring in 6% to 34% of KS patients with HIV who are initiating ART.[98,99] In sub-Saharan Africa, exacerbations of KS compatible with KS-IRIS have been reported in 18% to 61% of adults initiating ART treatment.[100-102] Risk factors for developing KS-IRIS include advanced KS tumor stage (T1), pre-treatment HIV viral load >5 $\log_{10}$ copies/mL, detectable pre-treatment plasma HHV-8, and initiation of ART alone without concurrent chemotherapy.[97] Treatment of KS-IRIS includes systemic chemotherapy and supportive measures. Steroids are strongly discouraged for management of KS-IRIS, as corticosteroid therapy has been associated with exacerbation of pre-existing KS in persons with HIV **(AIII)**.[70,103]

PEL: No data exist on the frequency with which initiation of ART complicates the course of primary effusion lymphoma.

MCD: A small number of patients with HIV-associated MCD have experienced clinical decompensation upon initiation of ART.[104,105]

Although neither the incidence nor predictors of HHV-8-associated IRIS are well-described, suppression of HIV replication and immune reconstitution are key components of therapy, and initiation of ART should not be delayed **(AIII)**.

Preventing Recurrence

Effective suppression of HIV replication with ART in patients with HIV and KS may prevent KS progression or occurrence of new lesions. Because KS is an AIDS-defining cancer, ART is indicated for all patients with active KS **(AII).** Suppression of HIV replication to prevent recurrence is also recommended for patients with MCD **(AIII)** as well as those with malignant lymphoproliferative disorders **(AIII).**

Special Considerations During Pregnancy

The seroprevalence of HHV-8 infection among pregnant women with HIV varies by geographic area, ranging from 1.7% among U.S.-born and 3.6% among Haitian-born women in New York City to 11.6% among pregnant women from 4 other U.S. cities.[106] Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels,[107] although levels of HHV-8 DNA in the peripheral blood may increase late in pregnancy.[108] HHV-8 seropositivity does not appear to influence pregnancy outcome. Routine screening for HHV-8 by PCR or serology is not indicated for pregnant women with HIV **(AIII).** Antiviral therapy for HHV-8 infection in pregnancy is not recommended **(AIII).** Given the rarity of KS, PEL, and MCD in pregnancy and the potential toxicity of the drugs used for treatment, when these conditions occur in pregnancy, they should be managed with consultations between the obstetrician, infectious disease specialist, and oncologist. With limited disease, treatment may be deferred until after delivery.[109]

In vitro models suggest that beta-human chorionic gonadotropin induces regression of KS tumors, but clinical reports on the incidence and natural history of KS in pregnancy are conflicting.[110-113] Perinatal transmission of HHV-8 occurs infrequently. Evidence supporting vertical transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth,[114,115] higher risk for transmission with higher maternal antibody titer (and, by inference, higher maternal levels of HHV-8),[116] and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants.[117] Data indicate increased mortality through age 24 months among infants with HIV born to HHV-8-seropositive mothers compared with HHV-8-seronegative mothers,[114-116,118-123] but these studies could not completely account for other confounding factors affecting infants with HIV. The majority of studies document a substantially higher rate of HHV-8 seropositivity among children born to HHV-8 antibody-positive compared with HHV-8 antibody-negative women.[118-123]

Recommendations for Preventing and Treating HHV-8 Diseases—Kaposi Sarcoma (KS), Primary Effusion Lymphoma (PEL), Multicentric Castleman's Disease (MCD)

Preventing development of KS:

- Since low CD4 cell count and uncontrolled HIV viremia are strong risk factors of KS, early initiation of ART is likely to be the most effective measure for the prevention of KS (**AII**)

Mild-to-Moderate KS (localized involvement of skin and/or lymph nodes)[1]:

- Initiation or optimization of ART (**AII**)

Advanced KS (visceral and/or disseminated cutaneous disease)[1]:

- Chemotherapy (*in consultation with specialist*) + ART [visceral KS (**AI**) or widely-disseminated cutaneous KS (**BIII**)].

- Liposomal doxorubicin is preferred first-line chemotherapy (**A1**)

- Avoid use of corticosteroids in patients with KS, including those with KS-IRIS, given the potential for exacerbation of life-threatening disease (**AIII**)

- Antiviral agents with activity against HHV-8 are not recommended for KS treatment (**AIII**).

PEL:

- Chemotherapy (*in consultation with a specialist*) (**AIII**) + ART (**AIII**)

- Oral valganciclovir or IV ganciclovir can be used as adjunctive therapy (**CIII**)

MCD:

All patients with MCD should receive ART (**AIII**) in conjunction with one of the therapies listed below.

Therapy Options (in consultation with a specialist, and depending on HIV/HHV-8 status, presence of organ failure, and refractory nature of disease):

- IV ganciclovir (or oral valganciclovir) +/- high dose zidovudine (**CII**)

- Rituximab +/- prednisone (**CII**)

- For patients with concurrent KS and MCD – rituximab + liposomal doxorubicin (**BII**)

- Monoclonal antibody targeting IL-6 or IL-6 receptor (**BII**)

- Corticosteroids are potentially effective as adjunctive therapy, but should be used with caution or avoided, especially in patients with concurrent KS. (**AIII**)

Other Considerations:

- Patients who receive rituximab or corticosteroids for treatment of MCD may experience subsequent exacerbation or emergence of KS

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenously; KS = Kaposi sarcoma; MCD = multicentric Castleman's disease; PEL = primary effusion lymphoma; PO = orally; q(n)h = every "n" hours

[1] The commonly used AIDS Clinical Trials Group (ACTG) KS Staging Classification uses T(Tumor), Immune(I), and Systemic illness (S) criteria to classify patients into "Good Risk" and "Poor Risk" categories (ref Krown, JCO, 1989). "Good Risk" tumor stage criteria are used by some specialists to correspond with mild-to-moderate KS.

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Human Papillomavirus Disease

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Recommendations for Cervical Cancer Screening for People With HIV

Recommendations for Anal Cancer Screening for People With HIV

Epidemiology

At least 12 human papillomavirus (HPV) types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[1-3] HPV68 is considered "probably oncogenic," and several other HPV types are considered "possibly oncogenic." HPV16 alone accounts for approximately 53% to 73% of cervical cancers in the general population and HPV18 for another 12% to 21%.[4] The other oncogenic HPV types each account for under 5% of cervical cancers.[4] Anal cancer and a subset of tumors of the vulva, vagina, penis, and oropharyngeal carcinoma (OPC) are also associated with HPV, and HPV16 and 18 are the most commonly detected in noncervical HPV-positive tumors.[2,5-14]

While anal cancer and OPC occur in both women and men with HIV, these two tumors disproportionally affect males with HIV, as well as African Americans.[15-18] Data also suggest that the distribution of oncogenic HPV types detected in cervical and anal cancers among people with HIV may differ from those in the general population.[19,20]

HPV infection is the major risk factor for development of cervical cancer,[5,21] the fourth most common cancer in women worldwide.[22] Nearly all cervical cancers contain oncogenic HPV DNA sequences.[23-25] While HPV is a common sexually transmitted cervical infection, most of these infections resolve spontaneously.[26-30] Cervical tumorigenesis occurs mostly, if not exclusively, in the presence of persistent oncogenic HPV infection.[1,5,31] Women with HIV have high incidence and persistence of HPV relative to women without HIV, as well as high rates of cervical intraepithelial neoplasia (CIN), cervical precancer (CIN 3), and invasive cancer.[32-40] Rates of cervical cancer in women with HIV were elevated significantly compared with the general population—3 to 4 times overall (95% confidence interval [CI], 3.13–3.70).[41] Most of these relative risks increase with decreasing CD4 T lymphocyte (CD4) cell counts, and cervical cancer is itself associated with advanced HIV.[42-54] The percentage with adenocarcinoma histology compared with squamous cell carcinoma is lower in women with HIV than in the general population. Several studies found decreased incident detection, persistence, and progression of HPV and CIN with effective

antiretroviral therapy (ART) use,[55,56] including one study that distinguished between adherent versus nonadherent or effective versus ineffective ART use (based on HIV RNA level).

In a report from the HIV/AIDS Cancer Match Study (2002–2016)—which included a population of 164,084 women with HIV—552 cases of invasive cervical cancer (ICC) occurred in 1.16 million person-years of follow-up (rate = 47.7 per 100,000). By age group, the highest incidence rates occurred in the 40- to 44- and 35- to 39-year-old age groups (rate = 66.1 and 64.5 per 100,000, respectively). No cases of ICC were identified in the under 25-year-old age group during 69,900 person-years of follow-up (standardized incidence ratio [SIR] = 0; 95% CI, 0,7.1).[41]

People with HIV have an increased incidence of anogenital tumors (vulva, vagina, penis) and OPC relative to the general population.[23,57-60] Low CD4 counts in people with HIV have been associated with increased risk of anal cancer,[61-63] as well as high-grade anal intraepithelial neoplasia (AIN; the likely anal cancer precursor lesion),[64-66] anal and genital warts, and vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).[67-69] Registry-based data indicate a downward trend in anal cancer incidence relative to the general population (i.e., a reduction in SIR from approximately SIR ~40 in 1996 to SIR ~20 in 2012; $P = 0.0001$),[59] as well as a possible ($P = 0.09$) decrease in cervical cancer from SIR ~5 in 1996 to SIR ~3 in 2012, and a nonsignificant decrease in OPC.[70,71] Other HPV-related tumors are less common, and less is known about trends in their incidence.

The elevated risk of HPV-associated cancers in people with HIV continues into older age (>50 years of age).[39] Registry-based data show that the 5-year risk (cumulative incidence) of anal cancer was 0.65% and 0.33% in men aged 45 to 59 years with HIV who have sex with men with and without AIDS, respectively, whereas the results were 0.10% and 0.04% for men with HIV who do not have sex with men, and 0.20% and 0.08% for women with HIV.[70] Similar results were obtained in a recent meta-analysis of available studies.[72] The ANCHOR study estimated the cumulative 4-year progression from high-grade squamous intraepithelial lesion (HSIL) to anal cancer was 1.8%.[73]

Anogenital warts have very low carcinogenic potential but are an important HPV-associated disease in people with HIV. These lesions are common, and more likely to be persistent in people with HIV than in the general population. Approximately 80% to 90% of anogenital warts are caused by non-oncogenic HPV types 6 or 11.[74] HPV types 6 and 11 also have been associated with conjunctival, nasal, oral, and laryngeal warts. In the United States, prior to the introduction of HPV vaccination, the incidence of anogenital warts was 60.2 per 10,000 women (aged 20–24 years) and 53.8 per 10,000 men (aged 20–24 years),[75-77] but with several-fold greater rates in people with HIV.[67] Low-grade vulvar lesions and genital warts were both found to decrease with ART.[67]

Clinical Manifestations

The principal clinical manifestations of mucosal HPV infection are genital, anal, and oral warts; CIN; VIN; VAIN; AIN; anogenital squamous cell cancers; and cervical adenocarcinomas. A subset of oropharyngeal cancers is also caused by HPV.[78]

Oral, genital (condyloma acuminata), and anal warts are usually flat, papular, or pedunculated growths on the mucosa or epithelium. The lesions may measure a few millimeters to 1 to 2 centimeters in diameter. Most warts are asymptomatic, but warts can be associated with itching or discomfort. In cases associated with more severe immunosuppression, marked enlargement may cause dyspareunia or dyschezia. Lesions of any size may cause cosmetic concerns.

Low-grade squamous intraepithelial lesions (LSIL) and HSIL in the cervix, vagina, vulva, and anal canal are often asymptomatic but may manifest with bleeding or itching. Related cancers also may be asymptomatic or may manifest with bleeding, pain, odor, or a visible/palpable mass. External lesions may be visible or palpable. Similarly, squamous cell cancers at these sites also can be asymptomatic or may manifest with bleeding, pain, or a visible/palpable mass.[79]

Preventing HPV Infection

Recommendations for Preventing HPV Infection
• HPV vaccine is recommended for routine vaccination at age 11 or 12 years.
o Administer three doses of 9-valent HPV vaccine (Gardasil 9) at 0, 1 to 2, and 6 months **(AIII)**. Ideally, the series should have been initiated at age 11 or 12 years but may be started as early as age 9 years. The two-dose series is not recommended in people with HIV.
• For all people with HIV aged 13 to 26 years who were not vaccinated previously:
o Administer three doses of 9-valent HPV vaccine (Gardasil 9) at 0, 1 to 2, and 6 months **(AIII)**. The two-dose series is not recommended in people with HIV.
• For people with HIV aged 27 to 45 years who were not adequately vaccinated previously:
o HPV vaccine is not routinely recommended; instead, shared clinical decision-making regarding HPV vaccination is recommended for people who may be at risk for a new HPV infection **(AIII)**.
• For people who were adequately vaccinated with bivalent or quadrivalent HPV vaccine:
o Some experts would consider additional vaccination with 9-valent HPV vaccine, but data are lacking to define the efficacy and cost-effectiveness of this approach **(CIII)**.
• HPV vaccination is not recommended during pregnancy **(CIII)**.

HPV Vaccine

HPV vaccination prevents HPV infection and is ideally administered before sexual exposure to HPV. Although HPV vaccine is most effective in people with few or no sex partners prior to vaccination, HPV vaccination in people with multiple lifetime sex partners can still prevent HPV infection from subtypes they have not been exposed to yet. Three U.S. Food and Drug Administration (FDA)–approved HPV vaccines are licensed: bivalent, quadrivalent, and 9-valent. Currently, only the 9-valent vaccine (9vHPV, protective against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) is available in the United States.[14,80] This vaccine has an FDA indication for prevention of cervical, vaginal, vulvar, and anal cancer; genital warts, and oropharyngeal and other head and neck cancers[81] based on randomized clinical trial (RCT) data; however, these studies were not conducted in people with HIV.[82-88] These RCTs evaluated several endpoints accepted by FDA and established the safety of the vaccine in children as young as 9 years of age and young people aged 16 to 26, as well as older women (aged 27–45 years).[89,90] Although no clinical trials have been conducted to demonstrate HPV vaccine efficacy in prevention of oropharyngeal cancers, some evidence exists that the prevalence of oral HPV infections from types contained in the vaccines are reduced with vaccination.[91,92] Protection against more subtypes might be more useful in people with HIV because there is more diversity of oncogenic subtypes of HPV.[14,80]

Routine HPV vaccination with the 9-valent vaccine should be initiated at age 11 or 12 years but may be started as early as age 9 years.[93,94] Although the Centers for Disease Control and

Prevention (CDC) Advisory Committee on Immunization Practices recommends a two-dose series,[95] the Panel recommends that people with HIV receive a three-dose series (0, 1–2, and 6 months) because their immune response to vaccination might be attenuated **(AIII).** Because HPV vaccination is safe and immunogenic and has the potential benefit of preventing HPV-associated disease and cancer, catch-up HPV vaccination is recommended for people with HIV aged 13 to 26 years **(AIII).** Although routine vaccination beyond age 26 is not recommended, shared clinical decision-making regarding HPV vaccination is recommended for adults aged 27 to 45 years who are not adequately vaccinated and are at risk for a new HPV infection **(AIII).**[94] Considerations to help guide shared clinical decision-making are available on the CDC website.

For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, some experts would give an additional full series (three doses) of vaccination with the 9-valent vaccine **(CIII),** however no data exist to define who might benefit or how cost-effective this approach might be.

Several studies have established the safety and immunogenicity of HPV vaccines in a broad range of people with HIV.[95-97] Some studies have demonstrated lower antibody levels in people with HIV than in those who do not have HIV; however, the clinical significance of this observation is unknown.[98-100] Studies have shown that HPV vaccination induces an anamnestic response in children and adults with HIV.[83,96,101] Immune responses appear stronger among those with higher CD4 counts and suppressed HIV viral loads.[97,102]

Although HPV vaccine clinical trials in people with HIV reported appropriate immunogenicity and safety,[95-104] few, if any, RCTs have utilized clinical endpoints, such as CIN 3 or incident persistent infection with vaccine HPV types. There is also a paucity of prospective epidemiologic studies using these endpoints.[105] One randomized, double-blind clinical trial evaluated the efficacy of the quadrivalent HPV vaccine (4vHPV) in a population of people with HIV who were older than 27 years with high rates of prior and current HPV infection. The trial did not show efficacy for prevention of new anal HPV infections or improvement in anal HSIL outcomes.[106] Anal cancer endpoints, including anal HSIL and anogenital wart incidence, were studied in another RCT of 4vHPV that involved 129 men who have sex with men (MSM) and who were on ART with a mean age of 38.8 years and who had history of AIDS.[107] Although the vaccine and placebo arms did not differ by HSIL or genital wart incidence, vaccine HPV types were less common in the vaccine arm, and in secondary analyses the investigators found that those with the longest time since immunization had significantly reduced risk of HSIL. A one-arm study of 260 MSM with HIV, aged 18 to 26 years, who received 4vHPV and were followed with high-resolution anoscopy at 7, 12, and 24 months found that no participants who were naive at baseline for one or more 4vHPV types developed LSIL or HSIL related to those HPV.[108] Conversely, a Phase 3 4vHPV RCT involving older males and females with HIV (aged ≥27 years) ended early due to an insufficient vaccine effect to meet stopping rules.[106] This trial did, however, suggest efficacy for short-term prevention of oral HPV infection, which decreased significantly from 88% to 32% after 6 months. A prospective observational cohort study of female youth who received 4vHPV showed unexpectedly high rates of abnormal cervical cytology, occurring in 33 of 56 youth who acquired HIV perinatally and only 1 of 7 of youth who were exposed but uninfected and yielding incidence rates of 100 person-years of 15 (10.9–29.6) and 2.9 (0.4–22.3), respectively. The majority of the diagnoses were LSIL or less, and the genotypes associated with these abnormal cytology results were unknown.[103]

People with HIV who have been vaccinated should continue routine cervical cancer screening because the vaccine does not prevent all HPV types that may be precursors to cervical cancer, and

because the vaccine may be less effective in people with HIV (especially those with low CD4 counts) than in people without HIV.

Condom Use

The use of male latex condoms is strongly recommended for preventing transmission or acquisition of HPV infection, as well as for preventing HIV and other sexually transmitted infections (STIs) **(AII).**[109-111] Latex condoms provide a sufficient barrier to prevent passage of particles the size of HPV. Consistent and proper use of latex male condoms has been associated with 70% lower incidence of oncogenic HPV infection among women.[111] Similarly, cross-sectional data suggested that among heterosexual men with no steady sex partner, consistent condom use was associated with 50% lower odds of HPV infection of the penis.[112] A meta-analysis found that condom use was associated with reduced risk of genital warts and, in women, with lower rates of CIN.[109] An RCT of condom use in heterosexual couples found significantly more frequent clearance of CIN and HPV among women randomized to condom use and of penile lesions among their male partners.[113,114] Male condoms have benefits in reducing risk of transmission of nearly all STIs (including HIV infection) during heterosexual intercourse and same-sex intercourse between men. In circumstances when a male condom cannot be used properly, a female condom (e.g., an FC1 or FC2 Female Condom) should be considered for heterosexual vaginal intercourse **(AII)** and for heterosexual or male same-sex anal intercourse **(BIII).** Data on FC1 and FC2 Female Condoms suggest that the devices are protective against STIs.[110]

Male Circumcision

There is evidence that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from RCTs and observational studies.[115-118] Observational studies in the general population also suggest that circumcision is associated with lower risk of penile cancer and of cervical cancer in sexual partners. Relevant data in men with HIV, however, are limited; findings to date suggest that the effects of circumcision against HPV infection (while protective) may be less in people with HIV than in those without. Furthermore, no clinical trials have assessed whether circumcision of men who have HIV reduces the risk of genital or anal HPV-related cancer or precancer (such as AIN) or oncogenic HPV infection of the anal or oral mucosa for them or their sexual partners. Evidence is insufficient to recommend adult male circumcision solely to reduce the risk of oncogenic HPV infection in men with HIV or their sex partners.

Preventing Disease

Cervical Cancer Screening Recommendations

Figure 1. Screening Algorithm for Cervical Cancer in People With HIV Aged 21 to 29 Years

Figure 2. Screening Algorithm for Cervical Cancer in People With HIV Aged 30 Years and Older

The same cytology and colposcopic techniques with biopsy are used to detect CIN among people with and without HIV (see section on Preventing Disease). At the time of cytology screening, the genitalia and anal canal should be inspected carefully for visual signs of warts or invasive cancer.

Available HPV tests can detect up to 14 oncogenic HPV types in clinical specimens and are sensitive for the detection of cervical cancer precursors. Some commercially available HPV tests will specify whether the oncogenic HPV includes genotypes HPV16 or HPV16/18. The available tests for oncogenic HPV have been incorporated into the screening algorithms. HPV testing is always for oncogenic HPV types only; there is no role for non-oncogenic HPV testing.

Observational epidemiologic studies in people with HIV have been instrumental in the decisions to adopt several cervical cancer screening guidelines that had been validated in large clinical trials in the general population. This included studies that supported the incorporation of cervical HPV testing for determining referral to colposcopy versus retesting in 1 year or during routine follow-up. For example, despite the very high prevalence of HPV in women with HIV, normal cytology with negative HPV co-testing had a strong negative predictive value, with low 3- to 5-year incidence of cervical intraepithelial neoplasia grade 2 (CIN 2+) regardless of CD4 count.[119,120] Conversely, the risk of precancer was high in women with HIV who tested positive for oncogenic HPV despite normal cervical cytology results and several-fold greater still if HPV16 was specifically detected.[121] Additional studies showed that oncogenic HPV testing had high sensitivity and negative predictive value in the triage of borderline cervical cytology results (i.e., atypical squamous cells of uncertain significance [ASC-US]).[122,123]

Possible cervical cytology results include the following:

- Normal (negative for intraepithelial lesion or malignancy)
- LSIL or CIN 1 (cervical intraepithelial neoplasia grade 1)
- HSIL or CIN 2, 3
- ASC-US
- ASC-H (atypical squamous cells, cannot rule out a high-grade lesion)
- AGC (atypical glandular cells)

For people with HIV, cervical cancer screening and treatment of precancer are, in and of themselves, a major burden. Positive HPV screening tests are several-fold more common in women with HIV than in the general population, and as many as 16% of women with HIV have abnormal cervical cytology with ASC-US or worse at each clinical visit.[124] This often leads to repeated colposcopy and biopsy, although most of these colposcopies and biopsies in people with HIV find LSIL rather than clinically relevant disease (e.g., HSIL, cancer). A study of "primary oncogenic HPV screening"— which uses HPV testing as the initial screening method and, if positive, often reflex-triage (e.g., HPV16/18-genotyping, cervical cytology)—found that this approach reduced unnecessary colposcopies by almost half relative to currently recommended HPV/cervical cytology co-testing for women with HIV.[125] However, these findings require confirmation. There is also a significant need for technical advancement to improve the positive predictive value of the screening tests—especially as many women with HIV exceed the age for routinely recommended HPV vaccination.[125]

People With HIV Aged 21 to 29 Years

Cervical cytology is the primary mode for cervical cancer screening for women with HIV under 30 years of age. People aged 21 to 29 years with HIV should have cervical cytology at the time of initial diagnosis with HIV **(AII).** See Figure 1. Screening Algorithm for Cervical Cancer in People With HIV Aged 21 to 29 Years for detailed recommendations. The absolute incidence of ICC is

exceedingly low among women with HIV under 25 years; therefore, cervical cancer screening is recommended to start at age 21. The rationale for beginning screening at age 21 is to provide a 3- to 5-year window prior to age 25, when the risk of ICC in women with HIV exceeds that of the general population.[41] Co-testing (cervical cytology and HPV test) and reflex high-risk HPV (hr-HPV) testing (HPV testing in the presence of abnormal cytology results) is routinely recommended for people without HIV and might be considered for people aged 25 to 29 years with HIV; however, there is a relatively high prevalence of transient HPV before age 30 years, which may lead to unnecessary colposcopy.[126] If cytology reveals ASC-US and reflex hr-HPV testing is performed, repeat cytology should be evaluated in 6 to 12 months **(AII).** If repeat cytology shows ASC-US and reflex hr-HPV is positive, individuals should be referred for colposcopy **(CIII).**

The American Society for Colposcopy and Cervical Pathology (ASCCP) and the American College of Obstetrics and Gynecology (ACOG) recommend screening for cervical cancer using cytology alone for women aged 21 to 29 years. The American Cancer Society (ACS) now recommends initiating cervical cancer screening at age 25 with primary HPV screening (hr-HPV testing alone) every 5 years in the general population. The FDA recently approved self-testing for HPV screening in clinical settings.[127] There are ongoing studies to evaluate the use self-testing for HPV screening in people with HIV. The U.S. Preventive Services Task Force (USPSTF) is reviewing its current recommendations and will issue an update soon regarding the use of primary HPV screening for cervical cancer.

People With HIV Aged 30 Years and Older

Cervical cancer screening in people with HIV should continue throughout their lifetime (and not, as in the general population, end at 65 years of age) **(BIII).** Either cytology only or cytology and HPV co-testing is acceptable for screening **(BIII).** See Figure 2. Screening Algorithm for Cervical Cancer in People With HIV Aged 30 Years and Older for detailed recommendations. Current guidelines from both the ACS and the USPSTF allow use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/HPV co-testing can allow a prolonged cervical cancer screening interval in women with HIV who are older than 29 years and have normal cervical cytology with concurrent negative HPV testing.

For people aged more than 65 years, it is recommended to continue cervical cancer screening because people with HIV are at higher risk for cervical cancer **(BIII).** However, clinicians should consider other factors, such as the life expectancy of the patient and the risk for developing cervical cancer at this age.[128]

Overview of Cervical Cancer Screening Guidelines					
	<21 Years	21–24 Years	25–29 Years	≥30 Years	Comments
NIH OAR Adult and Adolescent OI Guidelines (specific to people with HIV)	No screening recommended	**Cytology Only** • Cytology yearly ○ If normal cytology on 3 consecutive annual tests, adjust to every 3 years	**Cytology Only** • Cytology yearly ○ If normal cytology on 3 consecutive annual tests, adjust to every 3 years	**Co-testing[a]** • Co-testing yearly ○ If normal cytology and hr-HPV negative on 3 consecutive years, adjust to every 3 years. **Cytology Only** • Cytology yearly • If normal cytology on 3 consecutive years, adjust to every 3 years	
USPSTF (no HIV-specific guidance)	No screening recommended	• Cytology every 3 years	• Cytology every 3 years	**Cytology Only** • Every 3 years **hr-HPV Testing Only** • Every 5 years **Co-testing[a]** • Every 5 years	Not specific to people with HIV
ASCCP					Same as USPSTF
ACOG					Same as USPSTF
ACS (no HIV-specific guidance)	No screening recommended	No screening recommended	**Preferred** • Primary HPV test[b] every 5 years **Acceptable** • Co-testing every 5 years • Cytology alone every 3 years	**Preferred** • Primary HPV test[b] every 5 years **Acceptable** • Co-testing every 5 years • Cytology alone every 3 years	Updated July 2020 Not specific to people with HIV

Overview of Cervical Cancer Screening Guidelines					
WHO (HIV-specific guidance)	No screening recommended	No screening recommended	Preferred • Primary HPV test[b] (provider-obtained or self-collection) every 3–5 years	Preferred • Primary HPV test[b] (provider-obtained or self-collection every 3–5 years)	Updated July 2021

[a] Co-testing refers to combined cytology and high-risk HPV (hr-HPV) testing.

[b] Primary HPV testing is hr-HPV testing alone.

Key: ACOG = American College of Obstetricians and Gynecologists; ACS = American Cancer Society; ASCCP = American Society for Colposcopy and Cervical Pathology; HPV = human papillomavirus; hr-HPV = high-risk HPV; NIH OAR = National Institutes of Health Office of AIDS Research; OI = opportunistic infection; USPSTF = United States Preventive Services Task Force; WHO = World Health Organization

Preventing Vaginal and Vulvar Cancer

VAIN and VIN are recognized through visual inspection, including colposcopy and biopsy as needed. Most patients are asymptomatic, however. Abnormalities are usually detected after colposcopic examination and biopsy in response to abnormal cervical cytology. Following hysterectomy for benign disease, routine screening for vaginal cancer is not recommended for people with HIV **(AIII).** However, people with a history of high-grade CIN, adenocarcinoma *in situ*, or ICC are at increased risk and should be followed with annual vaginal cuff cervical cytology **(BIII).** For patients not known to have had a hysterectomy for a benign indication, continued screening is recommended since studies have shown that CIN is the most common indication for hysterectomy for people with HIV **(CIII).** Although vaginal cervical cytology results are often abnormal in women with HIV and more common than in women without HIV, VAIN 2+ and vaginal cancers are infrequent.[129] Another study in women with HIV with previous hysterectomy and no previous abnormal cervical cytology results, showed that among those with vaginal biopsies, 29% had VAIN 2 or VAIN 3.[130] However, this retrospective study was limited due to sample size. For patients with abnormal vaginal cuff cervical cytology results with no visible vaginal colposcopic abnormalities, the use of Lugol's iodine to stain the vagina is recommended **(AIII).** Vaginal colposcopy also is indicated in the presence of concomitant cervical and vulvar lesions. Classification of VAIN (i.e., VAIN 1, VAIN 2, and VAIN 3) parallels that of the cervix.

No screening procedure is available for vulvar cancer. However, biopsy or referral is indicated when inspection/palpation identifies lesions suspicious for VIN or cancer.

Screening for Anal Cancer

Figure 3. Screening Algorithm for Anal Cancer in Asymptomatic People With HIV

Figure 4. Assessment of Anal Cytology and HPV Results in People With HIV

Based on the high incidence of anal cancer in people with HIV, the high prevalence of anal HSIL in people with HIV, the high progression rate of anal HSIL to anal cancer in the absence of treatment, and efficacy in treating anal HSIL to reduce progression to anal cancer, screening for anal HSIL **(AII)**[73,131] and treatment of anal HSIL **(AI)** are recommended for people with HIV based on age.[73] See Figure 3. Screening Algorithm for Anal Cancer in Asymptomatic People With HIV and Figure 4. Assessment of Anal Cytology and HPV Results in People With HIV for detailed recommendations.

People with HIV, regardless of history of anal intercourse, should undergo annual assessment of anal symptoms (e.g., unexplained itching, anal bleeding, or pain; presence of perianal lesions). MSM and transgender women below the age of 35 and others below the age of 45 with anal symptoms should undergo digital anorectal examination (DARE) and standard anoscopy **(AIII).** See International Anal Neoplasia Society Guidelines for the Practice of Digital Anal Rectal Examination and Performing a Digital Anal Rectal Examination on how to perform a proper DARE.

MSM and transgender women aged 35 and above and all others with HIV aged 45 and above with symptoms or abnormal examinations should be referred to high-resolution anoscopy (HRA) if available **(BIII).** HRA identifies anal HSIL and (following biopsy for histopathologic confirmation) enables treatment of anal HSIL to prevent progression to anal cancer. If HRA is not available, patients should undergo standard anoscopy **(BIII)** and be referred for biopsy of identified lesions to determine level of histologic changes and to rule out invasive cancer**.** Standard anoscopy involves

visualization of the anal canal and perianal region through an anoscope without application of 5% acetic acid or Lugol's iodine to identify lesions. HRA requires specialized training and is performed with 5% acetic acid and Lugol's iodine to identify lesions under magnification typically provided by a colposcope. HRA allows flat lesions typical of HSIL or cancer to be identified with greater precision than standard anoscopy.

When to start screening for anal HSIL in asymptomatic individuals specifically should be based on the overall risk for anal cancer. The risk for anal cancer in people with HIV appears to differ based on age, sex at birth, and HIV exposure group, as evidenced by national estimates from the AIDS/Cancer Match Study, which links HIV/AIDS registries with data from the National Cancer Institute's Surveillance Epidemiology End Results (SEER), and by findings from a comprehensive meta-analysis of anal cancer screening and treatment studies (see figure on anal cancer incidence from this meta-analysis).[70,72]

Based on their incidence of anal cancer, and until definitive screening guidelines are available, experts in the field recommend that screening in asymptomatic people with HIV begin at different ages depending on sex and HIV risk group. Initiating screening for anal precancer and cancer is recommended at age 35 for MSM and transgender women who have HIV **(AII).** Screening for anal cancer should be initiated in cisgender women and all other persons with HIV at age 45 years **(AII).** MSM and transgender women aged 35 years and older, and other people with HIV aged 45 years and older, should continue to be assessed annually for anal symptoms and undergo DARE regardless of symptoms **(BIII).**

Older age, longer known duration of immune suppression and HIV infection, history of AIDS, smoking, positive HPV16 or 18 status, and higher grade of cytologic abnormality are associated with increased risk of anal cancer.[72,132-135] People with HIV who meet any of these criteria should be screened and referred for HRA as soon as feasible **(BIII).**

Screening can be performed using anal cytology alone or with hr-HPV co-testing. Screening individuals with anal cytology to identify those who need HRA with the goal of diagnosing and treating anal HSIL should be performed only when HRA and HRA-based treatment are available. There currently are no FDA-cleared anal HPV tests, but testing is available in many clinical laboratories. It is strongly recommended to use only clinical laboratories that have undergone CLIA certification to conduct anal HPV tests. If cytology will be obtained for screening, defer DARE until after swabbing anal canal to decrease potential for lubricant interfering with cytology results. Until further data on screening algorithms are available, the recommended screening approaches shown in Figure 3. Screening Algorithm for Anal Cancer in Asymptomatic People With HIV can be considered based on testing availability.

The International Anal Neoplasia Society (IANS) recently published recommendations for anal cancer screening including but not specific for people with HIV. We concur with the recommendation to screen for anal cancer for MSM and transgender women aged more than 35 years with HIV and all other people aged 45 years or above with HIV. We agree with the use of anal cytology or anal cytology with hr-HPV co-testing as screening modalities. In contrast to the IANS guidelines, we do not recommend HPV screening without cytology at this time due to insufficient supporting evidence in people with HIV **(BIII).** The prevalence of anal hr-HPV infection is very high among persons with HIV, and the specificity and positive predictive value for anal HSIL are expected to be low. Although screening for HPV16 or 18 specifically may improve the specificity and positive predictive value, anal cancer is associated with a broader spectrum of hr-HPV types in

people with HIV than in people without HIV; therefore, there may still be insufficient sensitivity for anal HSIL in people with HIV.[19]

Overview of Anal Cancer Screening Guidelines in People With HIV		
	NIH OAR Adult and Adolescent OI Guidelines	IANS Guidelines
Primary anal HPV testing alone without cytology as screening option	No	Yes
High-priority patients if HRA availability limited (no priority order specified in either guideline)	- Higher grade of cytologic abnormality - HPV16 on HPV testing - Smokers >60 years of age - Longer known duration of HIV - History of AIDS	- Higher grade of cytologic abnormality - HPV16 on HPV testing

Key: HPV = human papillomavirus; HRA = high-resolution anoscopy; IANS = International Anal Neoplasia Society; NIH OAR = National Institutes of Health Office of AIDS Research; OI = opportunistic infection

If HSIL is identified on biopsy, treatment of the lesion should be performed to reduce the incidence of anal cancer among people with HIV **(AI).** Further details are presented in the section "Treating AIN and Anal Cancer."

Preventing Oropharyngeal Cancer

Although HPV DNA detection might be useful in identifying individuals at high risk of oropharyngeal cancer, no adequate methods currently exist to determine the site of HPV-associated oropharyngeal precancer or cancer to target biopsy or treatment, despite ongoing efforts. It also should be noted that rates of non-HPV-associated oral cancer also are increased in people with HIV,[15] and potentially malignant oral disorders can be diagnosed and followed by biopsy in some cases; the effectiveness of this approach has not been tested in RCTs.[136]

Diagnosis

Warts/Condyloma

Diagnosis of genital and oral warts is made by visual inspection and can be confirmed by biopsy. However, biopsy is needed only if the diagnosis is uncertain, the lesions do not respond to standard therapy, or the warts are pigmented, indurated, fixed, bleeding, or ulcerated. No data support the use of HPV testing for screening, diagnosis, or management of visible genital/oral warts or oral HPV disease in people with HIV.[137]

Cervical Neoplasia

The same cytology and colposcopic techniques with biopsy are used to detect CIN among patients without HIV and people with HIV (see section on Preventing Disease). At the time of cytology

screening, the genitalia and anal canal should be inspected carefully for visual signs of warts, mucosal abnormalities that may indicate intraepithelial neoplasia, or invasive cancer.

Anal and Vulvar/Vaginal Neoplasia

AIN, VAIN, and VIN are recognized through visual inspection, including high-resolution anoscopy, colposcopy, and biopsy as needed. A digital examination of the anal canal to feel for masses should be performed as part of routine evaluation.[138]

Treating Disease

Cancer-specific survival following treatment of anal cancer and OPC was reported to be similar in people with HIV and the general population, whereas cervical cancer survival following treatment was reported to be lower in women with HIV.[139,140] Another study found that although response to initial therapy for ICC (e.g., radiation treatment) was similar in women with HIV compared with others, HIV was associated with higher risk of relapse (hazard ratio [HR] 3.6; 1.86–6.98) and higher cervical cancer mortality.[141] Data from the AIDS Malignancy Consortium showed that women with HIV on ART with locally advanced cervical cancer in sub-Saharan Africa can complete routine cisplatin and radiation therapy. Furthermore, 1-year progression-free overall survival rates observed among women with high-risk advanced tumors were similar to reported studies of women without HIV with generally smaller tumors.[142]

Treating Genital and Oral Warts

Patient-Applied Treatments Options

For Uncomplicated External Warts That Can Be Easily Identified by Patients

- Topical imiquimod (5% cream) at bedtime 3 nonconsecutive nights a week, for up to 16 weeks **(BII)**. Each treatment should be washed with soap and water 6 to 10 hours after application.

- Topical podofilox (0.5% solution or gel) twice a day for 3 days, followed by 4 days of no therapy. Can be repeated, as necessary, up to four times **(BIII)**.

- Topical sinecatechins (15% ointment) three times a day for up to 16 weeks until warts are cleared completely and not visible **(BIII)**

- Topical cidofovir 1% daily for 5 days per week for 8 weeks **(CIII)**. Not commercially available but may be compounded in pharmacies with required equipment.

Provider-Applied Treatment Options

For Complex or Multicentric Lesions, or Lesions Inaccessible to Patient, or Due to Patient or Provider Preference

- Cryotherapy (liquid nitrogen or cryoprobe) applied until each lesion is thoroughly frozen, with treatment repeated every 1 to 2 weeks for up to 4 weeks until lesions are no longer visible **(BIII)**. Some specialists recommend allowing the lesion to thaw and freezing a second time in each session **(BIII)**.

- TCA and BCA (80% to 90%) applied to warts only and allowed to dry until a white frosting develops. The treatment can be repeated weekly for up to 6 weeks, until lesions are no longer visible **(BIII)**.

- Intralesional cidofovir (15 mg/mL solution) injected directly into the wart (maximum 1 mL per session). May be repeated every 4 weeks for total of three to four treatments **(CIII)**.

- Surgical treatments (e.g., tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts **(BIII)**. Laser surgery is an option but is usually more expensive **(CIII)**.

Note: Many treatments for anogenital warts cannot be used in the oral mucosa. Surgery is the most common treatment for oral warts that interfere with function or for aesthetic reasons.

Considerations in Pregnancy

- Topical treatments such as BCA and TCA, as well as ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy **(AIII)**.

- Obstetrical management should not change for people with genital warts unless extensive condylomata might impede vaginal delivery or cause extensive bleeding **(AIII)**.

- Pregnant people should undergo cervical and anal cancer screening as recommended for nonpregnant people.

- Endocervical curettage is contraindicated in pregnant people **(AIII)**.

Key: BCA = bichloroacetic acid, TCA = trichloroacetic acid

Treating Genital and Oral Warts

People with HIV may have larger or more numerous warts, may not respond as well to therapy for genital warts as individuals who are immunocompetent, and may have more frequent recurrences after treatment. Genital warts are not life-threatening and may regress without therapy, even in people with HIV and especially in those whose immunity is relatively preserved. Treatments are available for genital warts, but none are effective or preferred uniformly. Lacking RCTs specific to people with HIV, guidelines for the treatment of STIs in people without HIV should be followed. More than one treatment option may be required for refractory or recurrent lesions in people with HIV. Histologic diagnosis should be obtained for refractory lesions to confirm the absence of high-

grade disease. Intra-anal, vaginal, urethral, or cervical warts should be treated and managed by a specialist.

Patient-applied treatments are recommended generally for uncomplicated external warts that can be identified easily and treated by the patient. Imiquimod (5% cream) is a topical cytokine inducer that should be applied at bedtime on 3 nonconsecutive nights per week, for up to 16 weeks, until lesions are no longer visible. The treatment area should be washed with soap and water 6 to 10 hours after the application **(BII).** Podofilox 0.5% solution or gel should be applied to visible anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, up to four times **(BIII).** Another option is sinecatechins (15% ointment), a topical botanical product that contains active catechins from green tea and should be applied three times daily for up to 16 weeks, until warts are cleared completely and not visible **(BIII).**[143] No clinical trials of this latter treatment option have been conducted in people with HIV. Topical application of cidofovir or intralesional cidofovir has reported activity against genital warts **(CIII).** Topical formulation is not commercially available but may be compounded in pharmacies with required equipment.[144-146]

Provider-applied treatments—such as cryotherapy, trichloroacetic acid (TCA), bichloroacetic acid (BCA), and surgery—typically are recommended for complex or multicentric lesions, lesions inaccessible to patient-applied therapy, or because of patient or provider preference.

Cryotherapy (liquid nitrogen or cryoprobe) destroys lesions by thermal-induced cytolysis and should be applied until each lesion is thoroughly frozen, with treatment repeated every 1 to 2 weeks for up to 4 weeks, until lesions are no longer visible **(BIII).** Some specialists recommend allowing the lesion to thaw and freezing a second time in each session **(BIII).**

TCA and BCA (80% to 90%) both act as caustic agents to destroy wart tissue and should be applied to warts only and allowed to dry until a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. The treatment can be repeated weekly for up to 6 weeks, until lesions are no longer visible **(BIII).**

Surgical treatments (e.g., tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts **(BIII).** Laser surgery is an option but is usually more expensive **(CIII).**

Intralesional interferon has been used for the treatment of genital warts, but because of cost, difficulty of administration, and potential for systemic adverse effects—such as fever, fatigue, myalgias, and leukopenia—it is not recommended for first-line treatment **(CIII).**

Podophyllin resin may be an alternative provider-applied treatment, with strict adherence to recommendations on application. It has inconsistent potency in topical preparations and can have toxicity that may limit routine use in clinical practice.

No consensus on optimal treatments of oral warts exists. Treatments for anogenital warts cannot be used in the oral mucosa. Given the lack of RCTs, surgical removal is the most common treatment for oral warts that interfere with function or need to be removed for aesthetic reasons.

These recommendations align with the CDC STI Treatment Guidelines.

Treating CIN and Cervical Cancer

People with HIV with CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in people with HIV should be managed according to ASCCP guidelines.

People with satisfactory colposcopy (transformation is fully visualized) and biopsy-confirmed high-grade CIN (CIN 2/3) can be treated with either ablation (e.g., cryotherapy, laser vaporization, electrocautery, diathermy, cold coagulation) or excisional methods (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization), whereas people with unsatisfactory colposcopy should be treated only with excisional methods **(AII).** In patients with recurrent high-grade CIN, diagnostic excisional methods are recommended **(AII).** Hysterectomy is acceptable for treatment of recurrent or persistent biopsy-confirmed high-grade CIN **(BII);** if invasive disease is suspected, the patient should be managed in consultation with a gynecologic oncologist. The ASCCP guidelines for adolescents and young women aged 21 to 24 years should continue to be followed. In these patients, progression of lesions is more common, and so is recurrence. Therefore, close observation, as outlined in the guidelines, should be considered for management of CIN 1; CIN 2; CIN 2,3 not otherwise specified (when pathology is HSIL but does not specify if CIN 2 or 3); and histologic HSIL in adolescents and adults with HIV who are younger than 25 years **(BIII).** If concern for loss to follow-up, excisional methods of treatment for CIN 2; CIN 2,3; and HSIL may be preferred **(BIII).**

Management of ICC may follow National Comprehensive Cancer Network (NCCN) guidelines. Although complication and failure rates may be higher in people with HIV, standard treatment appears safe and efficacious.[142]

Treating VIN, Vulvar Cancer, VAIN, and Vaginal Cancer

Low-grade VIN/VAIN (VIN/VAIN1) can be observed or managed the same as vulvovaginal warts. Treatment of high-grade VIN/VAIN should be individualized in consultation with a specialist and is dependent upon the patient's medical condition and the location and extent of the disease. Various treatment modalities are available for VIN, including local excision, laser vaporization, ablation, and topical therapies (e.g., imiquimod or cidofovir135 therapy). Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO_2 laser, and excisional procedures.[147-149]

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following NCCN guidelines.

Treating AIN and Anal Cancer

The ANCHOR study was not designed to compare different treatment modalities for efficacy. However, almost all participants were treated with office-based ablation of HSIL, most often hyfrecation. The rate of treatment-associated serious adverse events was very low. Office-based hyfrecation is therefore a reasonable first-line approach to treatment of anal HSIL **(AI).**[73] Those with anal cancer should be referred to Oncology for appropriate treatment.

Treating HPV-Associated Disease at Other Sites, Including the Penis and the Oropharynx

Penile and some oropharyngeal cancers are associated with HPV infection. Treatment options do not differ for men and women with and without HIV. Data suggest a more favorable prognosis for HPV-associated oropharyngeal cancers than for non-HPV-associated oropharyngeal cancers.[150-152] Surgery, chemotherapy, and radiation are treatment modalities used for oropharyngeal cancers.

Special Considerations Regarding Antiretroviral Therapy Initiation

Given the strong evidence that early ART initiation is clinically beneficial in reducing risk of AIDS and opportunistic infections (OIs), there is no reason to consider HPV-related oral, anal, or genital disease when deciding whether or when to initiate ART.

Monitoring Response to Therapy and Adverse Events (Including IRIS)

Monitoring by physical examination is required during and after treatment of genital warts to detect toxicity, persistence, or recurrence, all of which are common with each of the treatments. Because recurrences of CIN and cervical cancer after conventional therapy are more common with HIV, these individuals should be followed after treatment with frequent cytologic screening and colposcopic examination (see Preventing Disease and Treating Disease sections). Treatment of CIN with ablative and excisional modalities can be associated with several adverse events, such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis. Individualized treatment of adverse events is required.

Each of the treatment modalities for AIN described above is associated with adverse events, primarily pain, bleeding, ulceration, and, in rare cases, development of abscesses, fissures, or fistulas. Patients can be monitored for adverse events using the methods previously described.

Treatment for anal cancer with combination radiation and chemotherapy is associated with a high rate of morbidity, even when the treatment is successful. The most important complication is radiation-associated proctitis.

During IRIS, HPV may manifest as a paradoxical increase in warts after introduction of ART or by inflammation of existing warts.[153,154] A few studies also have shown the development of oral warts while starting ART.[155-158]

Managing Treatment Failure

For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered (**AIII**). Biopsy should be considered to exclude VIN. Genital warts often require more than one course of treatment.

Recurrent cytologic and histologic abnormalities after therapy for CIN should be managed according to ASCCP guidelines.

No consensus on the treatment of biopsy-proven recurrent VIN exists, and surgical excision can be considered.

Preventing Recurrence

Monitoring after therapy for cervical disease should follow ASCCP guidelines. In one study of women with HIV treated for high-grade CIN, low-dose intravaginal 5-FU (2 g twice weekly for 6 months) reduced the short-term risk of recurrence. Clinical experience with this therapy, however, is too limited to provide a recommendation for its use, and no follow-up study to confirm these observations has been reported. No guidelines exist regarding frequency of monitoring after therapy for VIN, but twice-yearly vulvar inspection appears reasonable for people who have been treated for VIN. People who have been treated for high-grade VAIN should be managed like those with CIN 2, that is, with cytology at 6 and 12 months after therapy, and annually thereafter.

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts, CIN, or AIN.

Special Considerations During Pregnancy

Pregnant people with HIV who have genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists, such as an obstetrician or gynecologist and an infectious disease provider. Pregnancy may be associated with an increased frequency and rate of growth of genital warts. Podofilox should not be used during pregnancy **(BIII).** At present, the evidence is insufficient to recommend imiquimod use during pregnancy. No anomalies have been observed with the use of imiquimod in animals during pregnancy. Several case series describe the use of imiquimod during pregnancy, also without any significant adverse effects.[159,160]

Other topical treatments—such as BCA and TCA—and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy **(AIII).**

Transmission of genital HPV6 and 11 from vaginal secretions at delivery is the presumed mechanism of juvenile-onset recurrent respiratory papillomatosis in children. This condition is rare but is seen more frequently among children born to women who have genital warts at delivery. Cesarean delivery is not known to prevent this condition in infants and children.[161] No change in obstetrical management is indicated for people with genital warts unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding **(AIII).**

Pregnant people should undergo cervical and anal cancer screening as recommended above for nonpregnant people. Cytobrush sampling can be done during pregnancy. Pregnant people with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of lesions suspicious for high-grade disease or cancer **(BIII).** Increased bleeding may occur with cervical biopsy during pregnancy. Endocervical curettage is contraindicated in pregnant people **(AIII).**

Pregnant people with ASC-US or LSIL can be managed the same as nonpregnant people, although deferral of colposcopy until at least 6 weeks postpartum is acceptable **(CIII).** Treatment of CIN is not recommended during pregnancy unless invasive disease is suspected **(AIII).** Pregnant people with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and development of a delivery plan. Vaginal delivery is not recommended for people with ICC **(AIII).** For people with CIN and without suspicion of invasive disease, re-evaluation with co-testing and colposcopy is recommended after 6 weeks postpartum **(AIII).** People with CIN can deliver vaginally.

Pregnancy testing is not needed before vaccination. HPV vaccination is not recommended during pregnancy **(CIII),** as there are limited data for its use in pregnancy; however, no intervention is needed if inadvertently given.[162] In a combined analysis of five RCTs of the HPV6/11/16/18 vaccine, administration of the vaccine to women who became pregnant during the course of the trial did not appear to negatively affect pregnancy outcomes.[163] Additionally, in a population-based study in Denmark, no increased risk of spontaneous abortion, stillbirth, or infant mortality was observed in more than 5,200 pregnancies exposed to at least one dose of the quadrivalent HPV vaccine. Also in Denmark, an analysis of the Medical Birth Register and National Patient Register found that among 1,665 exposed pregnancies, quadrivalent HPV vaccination was not associated with a significantly increased risk of adverse pregnancy outcomes, including major birth defect, preterm birth, or low birth weight.[164] Data on the use of the 9-valent vaccine during pregnancy are more limited, but to date are also reassuring.[165-169]

The effects of treatment of AIN on pregnancy are unknown. Most experts recommend deferral of diagnosis and treatment of AIN until after delivery unless a strong clinical suspicion of anal cancer exists.

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Immunizations for Preventable Diseases in Adults and Adolescents With HIV

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Overview

The Advisory Committee on Immunization Practices (ACIP) recommends immunizing people with HIV similarly to the general population, with a few key exceptions.

- The following live virus vaccines **are contraindicated** in people with HIV:
  - For CD4 T lymphocyte (CD4) cell count <200 cells/mm^3:
    - Measles
    - Mumps
    - Rubella
    - Varicella (VAR)
    - Live attenuated typhoid Ty21a
    - Yellow fever
  - For any CD4 counts:
    - Live attenuated influenza vaccine (LAIV)
- The following vaccines have specific recommendations related to HIV status:
  - COVID-19
  - Hepatitis A (HAV)
  - Hepatitis B (HBV)
  - Meningococcus serogroup A, C, W, Y (MenACWY)
  - Pneumococcal vaccines
  - Human papillomavirus

The National Institutes of Health/Infectious Diseases Society of America/HIV Medicine Association recommendations described here may differ from ACIP recommendations when the committees interpret data differently or when one guideline has been updated more recently than the other. Please see the Recommended Adult Immunization Schedule by Medical Condition and Other Indications table and Recommended Immunization Schedule for Adults and Adolescents With HIV figure at the end of this chapter for a full overview of vaccines for adults with HIV, including standard vaccines recommended for all individuals.

Specific Immunizations

COVID-19 Vaccine

Available Vaccines

- mRNA vaccines (Spikevax, Moderna; Comirnaty, Pfizer-BioNTech)

- Adjuvanted protein subunit vaccine (Novavax)

Summary of Recommendations

- For adults and children >5 years of age with HIV, administer a dose of the updated COVID-19 vaccine (once available) regardless of their CD4 count or HIV viral load **(AII).**

- Individuals with advanced or untreated HIV are considered moderately or severely immunocompromised and may receive one additional dose at least 8 weeks after the last COVID-19 vaccine dose **(AIII).**

  o Note: Advanced HIV is defined as people with CD4 count <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV.

- For current COVID-19 vaccination recommendations, please visit the Centers for Disease Control and Prevention (CDC) website on the [Use of COVID-19 Vaccines in the United States](#).

Evidence Summary

Worse outcomes for people with HIV and COVID-19, including high COVID-19 mortality rates, have been reported in cohort studies from the United States, the United Kingdom, and South Africa.[1-8] HIV was independently associated with an increased risk of severe and critical COVID-19 in a large trial from the World Health Organization's Global Clinical Platform, which included data from 38 countries.[9] In a multicenter cohort study of 286 people with HIV and COVID-19 in the United States, a lower CD4 count (i.e., <200 cells/mm^3) was associated with a higher risk for the composite endpoint of intensive care unit admission, invasive mechanical ventilation, or death. This increased risk was observed even in patients who had achieved virologic suppression of HIV.[6] Similarly, a multisite clinical cohort of people with HIV in clinical care in the United States showed an association between lower current (<350 cells/mm^3) and nadir (<200 cells/mm^3) CD4 counts and risk of hospitalization, intubation, or death, without an association between viral load suppression and COVID-19 disease severity.[10]

Most people with HIV develop antibody responses to vaccination comparable to those measured in people without HIV.[11-16] However, responses may be lower and antibody titers decline faster, particularly for individuals[13-15] with CD4 counts <200 cells/mm^3. Rates of breakthrough infections after vaccination are higher among individuals with HIV, with vaccine efficacy declining sooner than in HIV-negative matched cohorts.[17-19] Breakthrough infections showed no association with viral load suppression, though fewer breakthroughs[17] were seen in individuals with CD4 counts ≥500 cells/mm^3. Vaccine efficacy against more severe outcomes (e.g., hospitalization, intensive care unit admission, or death) has been more robust than protection against infection or mild disease.[20]

For individuals with advanced or untreated HIV, the lower seroresponse rates and reduced vaccine effectiveness compared to individuals without immunocompromise support recommendations for additional booster doses.[21]

Three COVID-19 vaccines are available in the United States: two mRNA formulations (Moderna and Pfizer) and one adjuvanted recombinant protein (Novavax). Since 2023, the original vaccines are no longer authorized and have been replaced with updated versions that better match circulating variants. Primary and booster vaccines have been harmonized to a single strain, and annual assessments are anticipated to update vaccine composition and scheduling recommendations.[22]

All adults and adolescents, regardless of their CD4 count or HIV viral load, should receive a dose of the newest updated COVID-19 vaccine when available (at least 4–8 weeks after last dose).[21,23] Those with severe immunosuppression may have a diminished immune response to the vaccine and therefore may receive one additional dose at least 8 weeks after the last COVID-19 vaccine dose. For current COVID-19 vaccination recommendations, please visit the CDC website on the Use of COVID-19 Vaccines in the United States.

Hepatitis A Vaccine

See the "Hepatitis A Virus (HAV)" section in the table below for detailed guidance on immunization against HAV.

Available Vaccines

- Single-antigen inactivated hepatitis A vaccines
  - HepA (Havrix, GSK)
  - HepA (Vaqta, Merck)
- Combination inactivated hepatitis A vaccine and recombinant hepatitis B vaccine
  - HepA-HepB (Twinrix, GSK)

Summary of Recommendations

For Vaccination

- Administer a two-dose series (dosing interval depends on the vaccine used: at 0 and 6–12 months for Havrix **[AII]** or 0 and 6–18 months for Vaqta **[AIII]**) of single-antigen hepatitis A vaccine (HepA) or a three-dose series (0, 1, and 6 months) of the combined hepatitis A and hepatitis B vaccine (HepA-HepB, Twinrix) to any person without evidence of immunity to HAV (and for the combined vaccine, without evidence of immunity to HAV or HBV) **(AII).**

- For travelers, some clinicians recommend a four-dose accelerated regimen (0, 7, 21–30 days, and 12 months) of HepA-HepB **(BII).**

- For people with HIV and CD4 count ≥200 cells/mm^3, assess antibody response 1 to 2 months after completion of the series. If negative, a third dose may be administered **(BIII).**

- People with HIV with CD4 count <200 cells/mm^3 who have ongoing risk for HAV should be immunized at entry to care and assessed for antibody response 1 to 2 months after completion of the series. If negative, revaccinate when their CD4 count is >200 cells/mm^3 **(BIII).**

- For people with HIV with CD4 count <200 cells/mm^3 who do not have ongoing risk for HAV, waiting for a CD4 count >200 cells/mm^3 prior to immunization is an option **(BIII).**

For Pre-Exposure Prophylaxis (Travel)

- For people with HIV who are nonimmune and traveling within 2 weeks to countries with endemic HAV, consider administering immunoglobulin G (IgG) 0.1 mL/kg if duration of travel is <1 month. If duration of travel is 1 to 2 months, administer IgG 0.2 mL/kg. If duration of travel is ≥2 months, IgG 0.2 mL/kg should be repeated every 2 months.

For Post-Exposure Prophylaxis

- For people with HIV who are nonimmune, administer HAV vaccine and IgG 0.1 mL/kg simultaneously in different anatomical sites as soon as possible, ideally within 2 weeks of exposure. Complete the HAV vaccine series following the dosing intervals for the selected vaccine.

Hepatitis B Vaccine

See the "Preventing Disease" section in Hepatitis B Virus (HBV) Infection for detailed guidance on immunization against HBV, as well as the evidence summary.

Available Vaccines

- Recombinant hepatitis B vaccine, CpG-adjuvanted
  - HepBCpG (Heplisav-B, Dynavax)
- Recombinant hepatitis B vaccines (conventional monovalent)
  - HepB (Engerix-B, GSK)
  - HepB (Recombivax HB, Merck)
- Combination inactivated hepatitis A and recombinant hepatitis B recombinant vaccine
  - HepA-HepB (Twinrix, GSK)

Summary of Recommendations

For Vaccination

- Indications for Hepatitis B Vaccination
  - People without chronic HBV infection and without immunity to HBV infection (negative for hepatitis B surface antigen, hepatitis B core antibody [anti-HBc], and hepatitis B surface antibody [anti-HBs]) **(AII).**
  - Although vaccine response is better in people with CD4 count >350 cells/mm^3, vaccination should not be deferred in people with a lower CD4 count who are at increased risk of acquiring HBV infection, because some people with CD4 <350 cells/mm^3 do respond to vaccination **(AII).**
- Preferred

- o Heplisav-B intramuscularly (IM) at 0 and 4 weeks **(AII)**

- Alternative (If HepBCpG [Heplisav-B] Is Unavailable)

  - o Engerix-B 40 mcg (two simultaneous injections of 20 mcg each) at 0, 1, and 6 months (these doses are considered a "double-dose," three-dose series) **(AII);** *or*

  - o Recombivax HB 20 mcg (two injections of 10 mcg each) at 0, 1, and 6 months (these doses are considered a "double-dose," three-dose series) **(AII);** *or*

  - o Twinrix combined HepA and HepB vaccine (1 mL IM) as a three-dose series (at 0, 1, and 6 months) **(AII)**

- Vaccination Schedule for Prior Non-Responders (Anti-HBs <10 mIU/ml) 1 Month After Complete Vaccine Series

  - o If prior Engerix-B or Recombivax HB vaccination failed, administer HepBCpG (Heplisav-B) IM at 0 and 4 weeks **(AI)** with consideration for a third dose of HepBCpG at 24 weeks **(BIII)**

  - o If prior two-dose HepBCpG (Heplisav-B) vaccination failed, there are no data but clinicians can consider a third dose of HepBCpG (Heplisav-B) IM at 24 weeks after first dose **(BIII).**

- Assess for Vaccine Response

  - o Anti-HBs should be obtained 4 weeks after completion of the vaccine series to document response to HepB vaccination, defined as anti-HBs ≥10 mIU/ml **(AII).**

- Vaccination Schedule for People With Isolated Anti-HBc

  - o One standard dose of any Hepatitis B vaccine followed by testing for quantitative anti-HBs 1 to 2 months post-dose.

    - ▪ If the titer is >100 mIU/mL, no further vaccination is needed.*

    - ▪ If the titer is ≤100 mIU/mL, a complete series of hepatitis B vaccine should be completed (see above for Vaccination Schedule), followed by repeat anti-HBs testing **(BII).**

    - ▪ If an anti-HBs quantitative titer is not available, then a complete hepatitis B vaccine series is recommended, followed by qualitative anti-HBs testing **(BII).**

    * See text in the Hepatitis B Virus (HBV) Infection regarding rationale for >100 mIU/mL.

For Post-Exposure Prophylaxis

- For people who have been exposed and were vaccinated previously with a complete HepB vaccine series and have documented antibody response, no additional vaccine is needed.

- For people who have been exposed and who received a complete HepB vaccine series without documentation of antibody response, administer a single dose of HepB vaccine.

- For people who have been exposed and have not received any HepB vaccine or have not received a complete HepB vaccine series, administer or complete an HepB vaccine series and administer one dose of hepatitis B immune globulin at a separate anatomical site as soon as possible after exposure (ideally within 24 hours, but up to 7 days after percutaneous exposure and up to 14 days after sexual exposure).

Human Papillomavirus Vaccine

See the "HPV Vaccine" section in Human Papillomavirus (HPV) Disease for detailed guidance on immunization against human papillomavirus (HPV), as well as the evidence summary.

Available Vaccine

- 9-valent inactivated recombinant vaccine (Gardasil 9, Merck)

Summary of Recommendations

- Routine HPV vaccination is recommended for people with HIV. Ideally, the series should be initiated at age 11 or 12 years but may be started as early as age 9 years. For all people with HIV who are aged 13 to 26 years and who were not vaccinated previously, regardless of gender, administer three doses of the recombinant HPV nonavalent vaccine (Gardasil 9) at 0, 1 to 2, and 6 months **(AIII).** The two-dose series **is not recommended** for people with HIV.

- Shared clinical decision-making regarding HPV vaccination is recommended for people with HIV who are aged 27 to 45 years and who were not adequately vaccinated previously **(AIII).**

- At present, vaccination with commercially available HPV vaccine **is not recommended** during pregnancy **(CIII).** However, in post-hoc analyses of clinical trials and population-based studies, HPV vaccines have not been linked to adverse pregnancy outcomes.[24-27]

- For people who have completed a vaccination series with the recombinant HPV bivalent or quadrivalent vaccine, some experts would consider additional vaccination with recombinant HPV nonavalent vaccine, but data are lacking for defining the efficacy and cost-effectiveness of this approach **(CIII).**

Influenza Vaccine

Available Vaccines*

- Inactivated Influenza vaccine (IIV3) (standard-dose, egg-based vaccine)
  - Afluria (Seqirus)
  - Fluarix (GSK)
  - FluLaval (GSK)
  - Fluzone (Sanofi Pasteur)
- ccIIV3 (standard dose, cell culture-based vaccine)
  - Flucelvax (Seqirus)
- HD-IIV3 (high-dose, egg-based vaccine)
  - Fluzone High-Dose (Sanofi Pasteur)
- aIIV3 (standard-dose, egg-based vaccine with MF59 adjuvant)
  - Fluad (Seqirus)
- RIV3 (recombinant hemagglutinin [HA] vaccine)

- o   Flublok (Sanofi Pasteur)
- LAIV3 (live attenuated, egg-based vaccine)
  - o   FluMist (AstraZeneca)

* Vaccine formulations are updated yearly to reflect circulating strains.

Summary of Recommendations

- For all adults and adolescents with HIV, administer age-appropriate inactivated influenza vaccine or recombinant influenza vaccine annually **(AI).**

- For pregnant people with HIV, administer inactivated influenza or recombinant vaccine at any time during pregnancy **(AI).**

- LAIV administered via nasal spray **is contraindicated** in people with HIV **(AIII).**

- High-dose, recombinant, and adjuvanted influenza vaccines are recommended for people with HIV aged 65 years or older over standard-dose unadjuvanted inactivated vaccines **(AII).**[28]

Evidence Summary

Influenza is a common respiratory disease in adults and adolescents. Annual epidemics of seasonal influenza typically occur in the United States between October and April. Influenza A and B are most frequently implicated in human epidemics. Influenza A viruses are categorized into subtypes based on characterization of two surface antigens: HA and neuraminidase (NA). Although vaccine-induced immunity to the surface antigens HA and NA reduces the likelihood of infection,[29,30] the frequent emergence of antigenic variants through antigenic drift[31] (i.e., point mutations and recombination events within a subtype) is the virologic basis for seasonal epidemics and necessitates revaccination each season.[32]

Some studies of influenza have noted higher hospitalization rates[33-36] and increased mortality[36,37] among people with HIV; however, these findings have not been observed in all settings.[38] Increased morbidity may be greatest for people with HIV not on antiretroviral (ARV) drugs or with advanced disease. People with HIV are at high risk of serious influenza-related complications. For more information, see the CDC's website on Flu and People Living With HIV.

In general, people with HIV with minimal AIDS-related symptoms and normal or near-normal CD4 counts who receive inactivated influenza vaccine (IIV) develop adequate antibody responses.[39-41] Among people with a low CD4 count or who have advanced HIV disease, IIV might not induce protective antibody titers.[41-43] In one study, markers of inflammation in older people (≥60 years) with HIV were associated with lower post-vaccination influenza antibody titers.[44] In people with HIV, a second dose of vaccine does not improve immune response,[42,45] and intradermal influenza vaccine dosing did not improve the immune response compared with intramuscular dosing.[46]

Influenza vaccines are trivalent (two A components and one B component) with formulations that change from season to season. Two clinical studies have evaluated influenza vaccine efficacy in people with HIV. In an investigation of an influenza A outbreak at a residential facility for people with HIV,[33] vaccination was most effective at preventing influenza-like illness among people with a CD4 count >100 cells/mm^3 and among those with HIV RNA <30,000 copies/mL. In a randomized placebo-controlled trial conducted in South Africa among 506 people with HIV, including

349 people on ARV treatment and 157 who were ARV treatment naive, efficacy of trivalent IIV for prevention of culture- or reverse transcription–polymerase chain reaction–confirmed influenza illness was 75% (95% confidence interval, 9% to 96%).[47]

Several clinical studies also have evaluated the immunogenicity of influenza vaccine in people with HIV. In a randomized study[48] comparing the immunogenicity of high-dose (60 mcg of antigen per strain) versus standard-dose (15 mcg of antigen per strain) trivalent IIV among 195 adults with HIV aged ≥18 years (10% of whom had a CD4 count <200 cells/mm^3), seroprotection rates were higher in the high-dose group for influenza A (96% vs. 87%; P = 0.029) and influenza B (91% vs. 80%; P = 0.030). However, in a comparative study of 41 children and young adults with HIV, high-dose trivalent IIV was no more immunogenic than the standard dose among the recipients with HIV.[49]

Although booster doses can make the influenza vaccine more effective, that benefit is limited to specific groups, such as solid-organ transplant recipients.[50] One study in people with HIV assessed the effectiveness of a two-dose regimen of IIV and found that the second dose of vaccine did not significantly increase the frequency or magnitude of antibody responses.[45] Based on this study, influenza booster immunizations **are not recommended** for people with HIV.

Optimally, influenza vaccination should occur before onset of influenza activity in the community because it takes about 2 weeks after vaccination for protective antibodies to develop.[28] Health care providers should offer vaccination by the end of October if possible, and vaccination should continue to be offered as long as influenza viruses are circulating. Information on currently available influenza vaccines is obtainable through the CDC. For adults aged ≥65 years, high-dose IIV,[51] adjuvanted IIV,[52] or recombinant influenza vaccine[53] are preferentially recommended over standard-dose unadjuvanted vaccines based on data suggesting higher efficacy in preventing invasive pneumococcal disease in this age group.[54]

Although a LAIV is available, it **is contraindicated** for people with HIV because of the paucity of safety data and the availability of alternative vaccines.[55] Although unintentional administration of LAIV to adults with HIV has been well tolerated,[56] **it is not recommended** for people with HIV.

IIVs can be administered to people receiving influenza antiviral drugs for treatment or chemoprophylaxis. Concurrent administration of influenza vaccine does not interfere with the immune response to other inactivated vaccines or to live vaccines.

Measles, Mumps, and Rubella Vaccine

Available Vaccines

- Live attenuated measles, mumps, and rubella (MMR) combination vaccine
  - M-M-R II (Merck)
  - Priorix (GSK)

Summary of Recommendations

For Vaccination

- Administer two doses of MMR vaccine at least 1 month apart to people with a CD4 count ≥200 cells/mm^3 and who have no evidence of immunity to MMR (evidence of immunity is

defined as: patient was born before 1957 and/or had documentation of receipt of MMR vaccine and/or has laboratory evidence of immunity or disease) **(AIII).**

- The MMR vaccine **is not recommended** during pregnancy.

- People of childbearing potential who get the MMR vaccine should wait 4 weeks before getting pregnant.

- For pregnant people without immunity to rubella, **delay immunization until after pregnancy,** and then administer two doses of the MMR vaccine at least 1 month apart if the CD4 count is ≥200 cells/mm^3 and on combination antiretroviral therapy (ART) **(AIII).**

- If no serologic evidence of immunity exists after two doses of MMR vaccine, consider repeating the two-dose MMR vaccine series, especially if the person is vaccinated while not virologically suppressed **(CIII).**

- **Do not administer** MMR vaccine to people with HIV with CD4 count <200 cells/mm^3 or uncontrolled HIV (not on ART or virologic failure) **(AIII).**

For Post-Exposure Prophylaxis

- For measles exposure of nonimmune individuals with CD4 count ≥200 cells/mm^3, administer the MMR vaccine within 72 hours of exposure **or** immunoglobulin (IG) within 6 days of exposure. Do not administer the MMR vaccine and IG simultaneously.

- For measles exposure of nonimmune individuals with CD4 count <200 cells/mm^3 or those who are pregnant, administer IG within 6 days of exposure.

Evidence Summary

Measles is a highly contagious and potentially life-threatening disease. Measles is particularly virulent in the immunocompromised host, with a reported mortality rate as high as 40% in people with advanced HIV.[57] Worldwide, the incidence of measles has continued to rise with several ongoing outbreaks. The World Health Organization reported that its European region experienced greater than 30,000 cases in 2022 up from fewer than 1,000 in 2021, and 51 countries had large disruptive outbreaks in 2023. The increase in cases is largely attributable to decreased rates of vaccination. Current information regarding outbreaks can be found on the CDC website Measles Cases and Outbreaks.[58]

With a resurgence of measles both domestically[59] and globally,[60] people with HIV should be assessed for immunity or prior vaccination. Acceptable evidence of immunity includes being born before 1957, documented evidence of two doses of the MMR vaccine, or presence of positive antibody titers.

Several studies from the 1990s found that 90% to 95% of adults with HIV were immune to measles.[61-63] In these studies, serostatus did not vary by CD4 count, suggesting that people with HIV retained protective immunity even in the context of advanced disease. However, in a more recent study, the measles seroprevalence rate was 70.3%. Similarly, people with HIV appear to retain immunity to mumps and rubella even after acquisition of HIV.[64]

Individuals who do not fulfill any criteria for immunity and have CD4 counts ≥200 cells/mm^3 should receive two doses of MMR vaccine separated by at least 28 days. The combination measles, mumps,

rubella, and varicella (MMRV) vaccine has not been studied in immunocompromised hosts and should **not be administered** to people with HIV.

The MMR vaccine **is contraindicated** for people with HIV with CD4 counts <200 cells/mm^3 because the MMR vaccine is a live attenuated formulation that has been linked to fatal cases of measles-associated pneumonitis following administration to people with HIV with a low CD4 count.[65,66] For people with HIV with CD4 count ≥200 cells/mm^3, the vaccine has been shown to be safe, although antibody response may be lower than for patients without HIV.[64,67,68] The MMR vaccine is also contraindicated for people with other immunocompromised conditions.

For more detailed information regarding post-exposure prophylaxis, please see the CDC webpage Measles (Rubeola).

Meningococcal Vaccine

Available Vaccines

- Quadrivalent meningococcal conjugate vaccine (MenACWY)
  - o Menveo (GSK)
  - o MenQuadfi (Sanofi Pasteur)
- Recombinant meningococcal group B vaccine (MenB)
  - o Bexsero (GSK)
  - o Trumenba (Pfizer)
- Pentavalent meningococcal vaccine (MenABCWY; combines conjugated MenACWY with recombinant MenB)
  - o Penbraya (Pfizer)

Summary of Recommendations

- Administer two doses of quadrivalent meningococcal conjugate vaccine (MenACWY) at least 8 weeks apart to adolescents and adults with HIV who have not been previously vaccinated **(AII).**

- For people with HIV who have been vaccinated previously, repeat vaccination every 5 years throughout life **(BIII).**

- Serogroup B meningococcal vaccination (MenB) is not routinely indicated for all people with HIV unless they have additional risks for meningococcal disease (e.g., complement component deficiency, asplenia, or receipt of a complement inhibitor) or are at risk during a serogroup B outbreak.

- Adolescents and young adults with HIV (age 16–23 years) can be offered MenB vaccination with shared decision-making **(CIII).**[69]

- Adults may receive a single dose of pentavalent meningococcal conjugate vaccine (MenABCWY) as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day **(BIII).**

Evidence Summary

Meningococcal meningitis, caused by *Neisseria meningitidis*, is the most common cause of bacterial meningitis among children and young adults in the United States. Surveillance data collected from 1998 to 2007 identified 2,262 cases of meningococcal disease from a sample of 13% of the U.S. population from several states. All available formulations of meningococcal vaccine are inactivated. Two MenACWY vaccines and one MenABCWY meningococcal vaccine are currently licensed and available in the United States: (1) meningococcal groups A, C, W, and Y oligosaccharide diphtheria CRM197 conjugate vaccine (MenACWY-CRM, Menveo); (2) meningococcal groups A, C, W, and Y polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT, MenQuadfi); and meningococcal groups A, C, W, and Y polysaccharide tetanus toxoid conjugate vaccine plus meningococcal group B recombinant FHbp antigens (MenACWY-TT plus MenB-FHbp; Penbraya). Meningococcal groups ACWY polysaccharide diphtheria toxoid conjugate vaccine (MenACWY-D, Menactra) is no longer available. A two-dose series of quadrivalent meningococcal vaccination is recommended for all adolescents with the first dose at 11 to 12 years and a second dose at 16 years. Adolescents and adults with HIV who have not had this primary meningococcal vaccination series should receive two doses of MenACWY vaccine at least 8 weeks apart **(AII).** Repeated MenACWY boosters are recommended every 5 years **(BIII).** MenACWY vaccines are licensed in the United States for one booster dose. Repeated boosters every 5 years is an off-label use but endorsed by ACIP.[70]

A growing body of evidence supports an increased risk of meningococcal disease in people with HIV. Studies have shown a five- to 24-fold increased risk of meningococcal disease in people with HIV compared with people without HIV[71-73]; low CD4 count and high HIV viral load are associated with increased risk.[74,75] From 2000 to 2011, the average annual incidence rate of invasive meningococcal disease was 0.39 cases per 100,000 people. People with HIV with a lower CD4 count are at higher risk of invasive disease.[74] Most meningococcal infections among people with HIV in the United States have been caused by serogroups C, W, or Y.[75] In addition, a cohort study found that uptake of the MenACWY vaccine among people with a new diagnosis of HIV infection was low, and time to receipt of first vaccination was long.[76]

The safety and immunogenicity of MenACWY-D vaccine have been evaluated only in people with HIV aged 11 to 24 years. Patients with CD4 percentage ≥15% received either one or two doses (at 0 and 24 weeks) of vaccine, and those with CD4 percentage <15% received two doses (at 0 and 24 weeks). Among people with HIV who received one dose of vaccine, 21% to 63% developed an antibody titer of ≥1:128 at 72 weeks after vaccination. Antibody responses at 72 weeks in individuals with CD4 percentage <15% were less robust,[77] with only 6% to 28% achieving titers ≥1:128. Local site reactions—such as pain and tenderness at the injection site—were uncommon (3.1%), as were grade 3 or greater events (2.2%). No vaccine-related deaths or cases of meningitis were noted. No safety or immunogenicity studies are available for quadrivalent MenACWY-CRM vaccine or the pentavalent vaccine in people with HIV, and clinical outcome data for both vaccines in people with HIV are lacking as well.

MenB is not routinely indicated for all people with HIV unless they have additional risks for meningococcal disease. Adolescents and young adults with HIV (age 16–23 years) can be offered MenB vaccination with shared decision-making **(CIII).**[69] MenB vaccine provides short-term protection against most strains of serogroup B meningococcal disease and has been used for patients at increased risk (e.g., those living in dormitories or barracks) and during outbreaks. People with functional or anatomic asplenia (including sickle cell disease), with persistent complement

component deficiency, or using a complement inhibitor (e.g., eculizumab, ravulizumab) should receive MenB vaccination.[70] Two MenB vaccines are available: MenB-4C (Bexsero; two-dose series given at 0 and 1 month) and MenB-FHbp (Trumenba; people with HIV should receive the three-dose series given at 0, 1–2, and 6 months rather than the two-dose option). MenB-FHbp consists of two purified recombinant lipidated FHbp antigens. MenB-4C consists of three recombinant proteins in addition to outer membrane vesicles that contain outer membrane protein porin A. MenB vaccines are not interchangeable; the same product must be used for all doses in the series. The pentavalent meningococcal vaccine contains the MenB-FHbp vaccine. A MenB vaccine booster may be indicated if a person previously vaccinated is identified as being at increased risk during a MenB outbreak. In this situation, a single dose of the same vaccine is recommended ≥1 year after the MenB primary series completion and every 2 to 3 years thereafter.

Urban outbreaks of meningococcal meningitis have been reported among men who have sex with men in the United States, in men both with and without HIV. Several outbreaks were associated with clubs and bathhouses. Some public health jurisdictions now recommend meningococcal vaccine for all men who have sex with men, regardless of HIV status; however, ACIP has not adopted this recommendation for men who have sex with men without HIV.[78]

Pregnant and lactating people with HIV should receive MenACWY vaccine if indicated **(AIII).** There have not been safety signals related to maternal and neonatal adverse events (including spontaneous abortion and birth defects) with MenACWY vaccine in clinical trial or in post-licensure surveillance.[79-83] Because limited data are available for MenB vaccination during pregnancy, vaccination with MenB should be deferred unless the pregnant person is at increased risk and, after consultation with their health care provider, the benefits of vaccination are considered to outweigh the potential risks **(CIII).**[70]

Mpox Vaccine

See the "Preventing Disease" section in Mpox for detailed guidance on immunization against mpox, as well as the evidence summary.

Available Vaccines

- Live nonreplicating smallpox and mpox vaccine
  - o JYNNEOS (Bavarian Nordic)

Summary of Recommendations

For Vaccination

- Mpox vaccination with live nonreplicating vaccinia vaccine, sold as JYNNEOS in the United States, should be offered to all people with HIV, including those who are pregnant or breastfeeding who have potential for mpox exposure or anticipate potential exposure to mpox per CDC interim clinical considerations **(BII),** as well as any other people with HIV who request vaccination **(CII).**

- JYNNEOS is the preferred vaccine before mpox exposure and is safe to use in people with HIV; administer JYNNEOS in two doses (0.5 mL subcutaneous [preferred] or 0.1 mL intradermal [alternative]) 4 weeks (28 days) apart **(AII).**

- If the second dose is not administered during the recommended interval, it should be administered as soon as possible **(CIII).** There is no need to restart or add doses to the series if there is an extended interval between doses **(CIII).**

- People who received smallpox vaccination more than 10 years ago should still receive two doses of JYNNEOS **(CIII).**

- Administration of live replicating vaccinia vaccines (i.e., ACAM2000) to pregnant, breastfeeding, or immunocompromised individuals, including people with HIV, **is contraindicated (AII).**

For Post-Exposure Prophylaxis

- For unvaccinated people with HIV who experience a known or presumed exposure, including to those who are pregnant or breastfeeding, administer a complete series of JYNNEOS as soon as possible, ideally within 4 to 14 days after exposure **(BII).**

For current information on the state of the outbreak and vaccination recommendation criteria, please visit the CDC's Mpox webpage. JYNNEOS has been demonstrated to be both safe for people with HIV and equally immunogenic compared with people without HIV.[84-86] However, these studies were limited to people who were virologically suppressed and had a CD4 count >100 cells/mm^3. Immunogenicity among people with HIV who are not virologically suppressed or have a lower CD4 count remains unknown.

Recent studies indicate that JYNNEOS is effective against mpox.[87-90] Matched case control study data indicate that vaccine effectiveness against symptomatic infection ranges from 36% to 75% after one dose to 66% to 89% after two doses.[90-93] However, all studies to date have had insufficient data to assess effectiveness of JYNNEOS against mpox by HIV status or CD4 count, and immunologic correlates of protection have not yet been established.

Pneumococcal Vaccine

See the "Preventing Disease" section in Community-Acquired Pneumonia for detailed guidance on immunization against pneumococcal disease, as well as the evidence summary.

Available Vaccines

- Pneumococcal conjugate vaccines (PCVs)
  - PCV15 (Vaxneuvance, Merck)
  - PCV20 (Prevnar 20, Pfizer)
  - PCV21 (Capvaxive, Merck)
- Pneumococcal polysaccharide vaccine (PPSV)
  - PPSV23 (Pneumovax, Merck)

Summary of Recommendations

For all people with HIV without a history of pneumococcal vaccination or with unknown vaccine history:

- Administer either 20-valent pneumococcal conjugate vaccine (PCV20) or PCV15 **(AII).**

- If PCV15 is used, administer a dose of PPSV23 at least 8 weeks later **(AII).** No additional pneumococcal vaccine doses are recommended.

For people with HIV who previously started or completed a pneumococcal vaccination series, there is no need to restart the series.

- People with HIV who received PCV13 and were 65 years or older when they received a dose of PPSV23 do not require further doses of PPSV23. Shared clinical decision-making is recommended regarding administration of PCV20 for adults aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23. If a decision to administer PCV20 is made, a dose of PCV20 is recommended at least 5 years after the last pneumococcal vaccine dose **(CIII).**

- For people with HIV who received PCV13 and were younger than 65 when they received a dose of PPSV23, one dose of PCV20 administered at least 5 years after may be used to complete their pneumococcal vaccinations **(CIII)** or additional doses of PPSV23 are recommended as indicated below **(BIII).**

  o People with HIV who have received PCV13 and PPSV23 at age <65 should receive a second dose of PPSV23 at least 5 years after the first dose. If they are age 65 or older at the time of their second dose, they do not require additional doses of PPSV23.

  o If they were <65 at the time of the second dose, they should receive a third and final dose at or after age 65, at least 5 years after the second PPSV23 dose.

- People with HIV who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose to complete their pneumococcal vaccination series **(BIII).**

- People with HIV who previously received only the PCV13 should receive one dose of PCV20 at least 1 year later **or** receive PPSV23 at least 8 weeks later and then complete the PPSV23 series as recommended above **(BIII).**

- In June 2024, the ACIP recommended 21-valent PCV (PCV21) as an option for adults aged ≥19 years who are currently recommended to receive PCV15 or PCV20. Data and recommendations for PCV21 are currently under review in this guideline.

Respiratory Syncytial Virus

Available Vaccines

- Adjuvanted protein subunit vaccine (Arexvy, GSK)

- Bivalent protein subunit vaccine (Abrysvo, Pfizer)

- mRNA vaccine (mRESVIA, Moderna)

Summary of Recommendations

- Administration of a single respiratory syncytial virus (RSV) vaccine (Abrysvo, Arexvy, or mRESVIA) to all people with HIV ≥75 years old is recommended **(CIII).**

- Administration of a single RSV vaccine for people ages 60 to 74 with HIV and CD4 <200 cells/mm^3 or with comorbid chronic [conditions that increase risk for severe RSV disease](#) is recommended.

- For pregnant people with HIV, administration of a single RSV vaccine (Abrysvo) between 32 and 36 weeks gestation with seasonal administration during September through January in most of the continental United States is recommended **(CIII).**

- No booster doses are currently recommended **(CIII).**

Evidence Summary

RSV is a significant cause of lower respiratory tract infection and bronchiolitis worldwide in children <5 years and adults ≥60 years of age. RSV vaccine development began in the 1960s; however, early formaldehyde-inactivated RSV vaccines induced a life-threatening inflammatory response during subsequent natural RSV infection in infants.[94] Following an improved understanding of the structure of RSV, modern vaccine research has developed a myriad of safer approaches including live attenuated, chimeric, vector-based, subunit proteins, nanoparticle, and nucleic acid vaccines.[95] Currently there are at least 19 RSV vaccines in clinical trials evaluating efficacy in pediatric, pregnant, and adult populations.[96]

In May 2023, the United States Food and Drug Administration approved the first two RSV vaccines for adults ≥60 years of age: RSVPreF3 (Arexvy) and RSVpreF (Abrysvo). Both vaccines target the prefusion F protein on the viral surface.[97]

RSVPreF3 (Arexvy) is an AS01$_E$-adjuvanted RSV prefusion F protein–based vaccine, approved based on results of a large clinical trial comparing the candidate vaccine to placebo over a median follow up of 6.7 months.[98] The study included 17,922 participants. People with HIV were excluded from the study. Relative to placebo, RSVPreF3 was efficacious in reducing RSV-related lower respiratory tract disease, severe lower respiratory tract disease, and acute respiratory infection by 83%, 94%, and 72%, respectively. Further, this vaccine was generally safe with most adverse events being transient, mild to moderate, and related to local pain and fatigue. Rare inflammatory neurologic events were reported in three trial participants within 42 days of receipt of the RSVPreF3; all events occurred in trials without a placebo arm. These included one case of Guillain-Barré syndrome (GBS) and two cases of acute disseminated encephalomyelitis (ADEM). Both ADEM cases were based on symptoms and clinical findings, and one case was fatal.

RSVpreF (Abrysvo) is a bivalent RSV prefusion F protein–based vaccine that demonstrated efficacy in a large, randomized clinical trial with a mean follow up of 7 months.[99] Immunocompromised patients were excluded from this trial. People with well-controlled HIV (viral load <50 copies/mL and CD4 counts >200 cells/mm^3 on ART) were eligible, but the number of people with HIV in the trial is not reported. Compared to placebo, RSVpreF reduced RSV-related lower respiratory tract illness with at least two signs or symptoms and with at least three signs or symptoms, by 67% and 86%, respectively. RSVpreF reduced RSV-associated acute respiratory illness by 62%. RSVpreF was relatively safe with higher rates of local reactions in the vaccine (12%) versus placebo (7%), but rates of systemic events were similar. Rare inflammatory neurologic events were reported in three of 34,284 participants, including one case of GBS, one case of Miller Fisher syndrome (GBS variant), and one case of undifferentiated motor-sensory axonal polyneuropathy. A separate clinical trial evaluated RSVpreF versus placebo in pregnant people to determine efficacy in reducing RSV-related illness in newborns and infants.[100] In interim analysis, RSVpreF was effective in reducing medically

attended severe RSV-associated lower respiratory tract illness in infants within 90 days after birth, and no safety concerns were identified. Pregnant people with HIV were excluded from this trial.

mRNA-1345 (mRESVIA) is an mRNA-based RSV vaccine encoding the stabilized RSV prefusion F glycoprotein. In a trial of more than 35,000 participants 60 years and older, the vaccine demonstrated greater than 80% efficacy against RSV-related lower respiratory tract disease.[101] Participants with HIV and CD4 count ≥350 cells/mm^3 and an undetectable HIV viral load within the past year were permitted to enroll in the trial. The vaccine was generally well tolerated, and no cases of ADEM or GBS were observed.

In June 2024, the ACIP recommended that adults 75 years and older and adults 60 to 74 with comorbid conditions that increase risk for severe RSV disease receive a single dose of an approved RSV vaccine. A full list of qualifying conditions can be found on the CDC webpage.[102] In September 2023, the ACIP and the American College of Gynecology both recommended seasonal administration of one dose of RSV vaccine for pregnant people during weeks 32 through 36 of pregnancy, ideally at least 14 days before delivery.

In the absence of additional data regarding immunologic response, clinical efficacy, and safety in patients with HIV, these recommendations are aligned with the ACIP guidance for the general population. For people with HIV, offer a single RSV vaccine (Abrysvo, Arexvy, or mRESVIA) to individuals aged ≥75 years and those between 60 to 74 with qualifying comorbid conditions **(CIII).** Individuals aged 60 to 74 with HIV and CD4 <200 cells/mm^3 are eligible for RSV vaccination, although the vaccines have not been studied in this population, and many clinicians may choose to wait for immune reconstitution prior to administering the vaccine **(CIII).** Optimally, vaccination should occur before the onset of the fall and winter RSV season.

For pregnant people with HIV, administer a single RSV vaccine (Abrysvo) between 32 to 36 weeks gestation with seasonal administration during September through January in most of the continental United States **(CIII).** The adjuvanted vaccine, Arexvy, and the mRNA vaccine, mRESVIA, have not been studied in pregnancy and should not be used as an alternative. In locations where the seasonality of RSV differs from the continental United States (e.g., tropical climates, the Southern hemisphere), providers should follow local guidance on timing of administration. Data regarding immunologic response to the vaccine and clinical outcomes are notably lacking in people with HIV.

Tetanus, Diphtheria, and Pertussis Vaccine

Available Vaccines

- Tdap: Tetanus, diphtheria, and pertussis
  - Adacel (Sanofi Pasteur)
  - Boostrix (GSK)
- Td: Tetanus and diphtheria
  - TENIVAC (Sanofi Pasteur)

Note: DTaP vaccines (diphtheria, tetanus, and pertussis) are only for babies and young children and therefore are not covered in these guidelines.

Summary of Recommendations

- Administer the combination tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) once if the person with HIV has not been vaccinated at age 11 or older, and then tetanus and diphtheria toxoids vaccine (Td) or Tdap every 10 years thereafter **(AII).**

- For pregnant people with HIV, administer one dose of Tdap during each pregnancy, preferably between 27 weeks and 36 weeks gestation **(AIII).**

- For adolescents and adults with HIV who have not received the primary vaccination series for tetanus, diphtheria, or pertussis, administer one dose of Tdap followed by one dose of Td or Tdap at least 4 weeks after Tdap, and another dose of Td or Tdap 6 months to 12 months after the last Td or Tdap. Tdap can be substituted for any Td dose and is always preferred as the first dose **(AIII).**

Evidence Summary

Antibody response to tetanus and diphtheria vaccination varies by CD4 count. For individuals with advanced HIV and a low CD4 count, immunologic response is attenuated for both tetanus and diphtheria when compared to HIV-uninfected controls.[103,104] For people with CD4 count >300 cells/mm^3, antibody response to tetanus vaccination is similar to the general population, whereas response to diphtheria remains diminished.[103-105] Limited data exist on the efficacy of pertussis vaccination in this population.

Two Tdap vaccines for individuals aged ≥10 years are available in the United States (Adacel and Boostrix). Both vaccines are inactivated and considered safe to administer at any CD4 count. People with HIV should receive vaccination for tetanus, diphtheria, and pertussis on the same schedule as individuals without HIV. All adults not previously vaccinated should receive a single dose of Tdap, followed by a Td or Tdap booster every 10 years.

Varicella Vaccine

See "Vaccination to Prevent Primary Infection (Varicella)" in the Varicella-Zoster Virus Disease section for detailed guidance on immunization against varicella, as well as the evidence summary.

Available Vaccines

- Live attenuated varicella vaccine
  - Varivax (Merck)

Summary of Recommendations

- People with HIV with any of the following have presumed immunity to varicella: receipt of two doses of varicella vaccine (Varivax or MMRV), diagnosis of varicella or herpes zoster (shingles) by a health care provider, or laboratory evidence of immunity or disease.

- For people with HIV who are varicella nonimmune with CD4 count ≥200 cells/mm^3, administer two doses of varicella vaccine (VAR) 4 to 8 weeks apart **(BIII).**

- VAR is **contraindicated** for people with HIV with CD4 count <200 cells/mm^3 **(AIII).**

- VAR **is not recommended** during pregnancy **(AIII).**

Herpes Zoster Vaccine

See "Vaccination to Prevent Reactivation Disease (Herpes Zoster)" in the Varicella-Zoster Virus Disease section for detailed guidance on immunization against zoster, as well as the evidence summary. Herpes zoster vaccine has not been studied for prevention against primary varicella infection.

Available Vaccines

- Recombinant adjuvanted zoster vaccine (RZV)
  - Shingrix (GSK)

Summary of Recommendations

- For people with HIV ≥18 years, administer two doses of RZV at 0 and 2 to 6 months **(AIII).**

- Consider delaying vaccination until the patient is virologically suppressed on ART **(CIII)** or until the CD4 count is ≥200 cells/mm^3 to ensure a robust vaccine response **(CIII).**

- People with HIV ≥18 years should receive RZV regardless of previous history of herpes zoster or previous receipt of zoster vaccine live (no longer available).

- Do not give RZV (Shingrix) during an acute episode of herpes zoster **(AIII).**

- RZV **is not recommended** during pregnancy **(AIII).**

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
COVID-19	All people regardless of CD4 count or viral load **(AII)**	People with HIV should receive a complete COVID-19 vaccine series regardless of their CD4 count or HIV viral load or their pregnancy or breastfeeding status **(AIII)**. For current COVID-19 vaccination recommendations, please visit [CDC.gov](CDC.gov).	People with advanced or untreated HIV are considered moderately or severely immunocompromised and may get a second dose of the updated vaccine at least 8 weeks after the first **(AIII)**.	No difference in recommendations
Hepatitis A Virus (HAV)	HAV nonimmune **(AIII)**	Two-dose series of either single-antigen vaccine: • Havrix: 1.0 mL IM (0, 6–12 months) **(AII)**; or • Vaqta: 1.0 mL IM (0, 6–18 months) **(AIII)** Alternative for individuals susceptible to both HAV and HBV: • Twinrix: 1.0 mL IM in three-dose series (0, 1, 6 months) **(AII)**	Assess total antibody response (IgG and IgM) 4 weeks after completion of the series, and if negative, revaccinate, preferably after the CD4 count is ≥200 cells/mm³ **(BIII)**. For travelers, some clinicians recommend— • Twinrix: four-dose series (0, 7, 21–30 days, 12 months) **(BII)**	No difference in recommendations
	Post-exposure prophylaxis	Administer HAV vaccine and HepA IgG (0.1 mg/kg) simultaneously in different anatomical sites as soon as possible within 2 weeks of exposure to HAV to people who are nonimmune. Complete the HAV vaccine series following the dosing intervals for the selected vaccine.		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Hepatitis B Virus (HBV)	HBV nonimmune and no active HBV (i.e., negative for HBsAg, anti-HBc, and anti-HBs)	Preferred: • Heplisav-B IM at 0 and 4 weeks **(AII)** Alternative (if Heplisav-B is unavailable): • Engerix-B (40 mcg): three-dose series (0, 1, 6 months) **(AII)**; *or* • Recombivax HB (20 mcg): three-dose series (0, 1, 6 months) **(AII)**; *or* • Twinrix 1.0 mL IM: three-dose series (0, 1, 6 months) **(AII)**	Anti-HBs should be obtained 4 weeks after completion of the vaccine series to document response to HepB vaccination, defined as anti-HBs ≥10 mIU/mL **(AII)**. Vaccinate individuals with isolated anti-HBc with one standard dose of HepB **(BII)** and check anti-HBs titers 1–2 months afterward. If anti-HBs ≥100 mIU/mL, no further vaccination is needed, but if the titer is <100 mIU/mL, then vaccinate with a complete series of HepB (double dose) followed by anti-HBs testing **(BII)**. If titers are not available, then give a complete vaccine series followed by anti-HBs testing **(BII)**. If a significant delay occurs between doses, there is no need to restart the series. For travelers, some clinicians recommend an accelerated schedule: • Twinrix: four-dose series (0, 7, 21–30 days, 12 months) **(BII)** Some experts consider that a four-dose vaccine series of recombinant HepB vaccine (Engerix-B 40 mcg or Recombivax HB 20 mcg at 0, 1, 2, and 6 months) may produce a better immunologic response, but this approach has not been demonstrated to be superior to a double-dose, three-dose series.	ACIP does not recommend the use of double-dose Engerix-B or Recombivax HB high-dose for people with HIV.
	Vaccine nonresponder (if anti-HBs <10 mIU/mL after complete series)	If failed prior Engerix-B or Recombivax HB: • Heplisav-B IM at 0 and 4 weeks **(AI)** with consideration for third dose of HepBCpG at 24 weeks **(BIII)** If failed two-dose Heplisav-B, there are no data but can consider: • Third dose of Heplisav-B IM at 24 weeks after first dose **(BIII)**		
	Post-exposure prophylaxis	For exposed people who have been previously vaccinated with a complete series and have documented antibody response, no additional vaccine is needed.		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
		For exposed people who have received complete series without documentation of antibody response, administer a single dose of HepB vaccine. For exposed people who have not received a vaccine or have not received the complete series, administer or complete the HepB vaccine series and administer a dose of HBIG at a separate anatomical site as soon as possible after exposure (ideally within 24 hours, but up to 7 days after percutaneous exposure and up to 14 days after sexual exposure).		
Human Papillomavirus (HPV)	Adults and adolescents through age 26 years	Recombinant 9-valent human papillomavirus vaccine (Gardasil 9): • 0.5 mL IM three-dose series (0, 1–2, and 6 months) **(AIII)**	If a significant delay occurs between doses, there is no need to restart the series. Some people with HIV ages 27–45 years may benefit from vaccination, and shared clinical decision-making between the provider and patient is recommended in these situations. Vaccination is **not recommended** during pregnancy **(CIII)**. Delay until after pregnancy.	No difference in recommendations

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Adults and adolescents who previously received bivalent or quadrivalent vaccine	For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, no recommendations exist for additional vaccinations; some experts would give an additional full series of recombinant 9-valent vaccine, but no data currently define who might benefit or how cost effective this approach might be **(CIII)**.		
Influenza	All	One dose of age-appropriate IIV or RIV annually **(AI)** LAIV **is contraindicated (AIII)**.	Information on currently available influenza vaccines is available through the CDC. Influenza vaccines are trivalent, with formulations that change from season to season. Adults age ≥65 years are recommended to receive high-dose IIV (Fluzone High-Dose), RIV (Flublok), or adjuvanted IIV (FLUAD) over standard-dose unadjuvanted vaccine **(AII)**. People ages ≥18 years also may use RIV (Flublok). For people with egg allergy, use IIV or RIV appropriate for age (if the allergy is more severe than hives, give the vaccine in a medical setting appropriate to manage severe allergic reaction). For pregnant people with HIV, administer IIV or RIV at any time during pregnancy **(AI)**.	No difference in recommendations

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Measles, Mumps, and Rubella (MMR)	CD4 count ≥200 cells/mm^3 and no evidence of immunity to MMR	Two-dose series (0.5 mL SQ) of MMR vaccine at least 1 month apart **(AIII)** MMR vaccine **is contraindicated** if CD4 count <200 cells/mm^3 **(AIII).** MMR vaccine **is not recommended** during pregnancy.	Evidence of immunity to MMR vaccine • Birth date before 1957, *or* • Documentation of receipt of MMR vaccine, *or* • Laboratory evidence of immunity or disease for each pathogen For pregnant people without immunity to rubella, after pregnancy, administer two doses of MMR vaccine at least 1 month apart if CD4 count ≥200 cells/mm^3 and on ART **(AIII).**	No difference in recommendations
	Post-exposure prophylaxis	For measles, nonimmune individuals with CD4 count ≥200 cells mm^3, administer MMR vaccine within 72 hours of exposure **or** IG within 6 days of exposure. Do not administer MMR vaccine and IG simultaneously. For measles, nonimmune individuals with CD4 count <200 cells mm^3 or those who are pregnant, administer IG within 6 days of exposure.		
Meningococcus Serogroup A, C, W, Y (MenACWY)	No prior polyvalent meningococcal vaccine	MenACWY vaccine (Menveo or MenQuadfi): • Two-dose series (0.5 mL IM) given at least 8 weeks apart **(AII)**	MenACWY vaccine is routinely recommended. Pregnant and lactating people with HIV should receive MenACWY vaccine if indicated **(AIII).**	No difference in recommendations

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Prior MenACWY vaccination	Administer a booster dose of MenACWY vaccine every 5 years **(BIII)**. MenABCWY vaccine should be used if MenACWY and MenB vaccines are both indicated **(BIII)**.	MenACWY vaccines are interchangeable; the same vaccine product is recommended, but not required, for all doses.	
Meningococcus Serogroup B (MenB)	No prior MenB vaccine and increased risk for serogroup B meningococcal disease from a medical condition (e.g., complement component deficiency, asplenia, or receipt of a complement inhibitor) or an outbreak	Administer either MenB vaccine: • Two-dose series (0.5 mL IM) of Bexsero given at least 1 month apart **(AIII)**; *or* • Three-dose series (0.5 mL IM) of Trumenba administered at 0, 1–2, and 6 months **(AIII)**	MenB vaccines (Bexsero and Trumenba) are not interchangeable. MenB vaccination during pregnancy should be deferred **(CIII)**.	No difference in recommendations
	Prior MenB vaccination (≥1 year) and at increased risk during an outbreak	Administer booster dose of same MenB vaccine **(CIII)**.	Licensed in the **United States** only for a primary series. Administration of booster doses is considered off-label.	
	Adolescents and young adults with HIV (age 16–23 years) can be offered MenB vaccination with shared decision-making.	Administer either MenB vaccine: • Two-dose series (0.5 mL IM) of Bexsero given at least 1 month apart **(CIII)**; *or* • Three-dose series (0.5 mL IM) of Trumenba administered at 0, 1–2, and 6 months **(CIII)**		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Mpox	All people who have potential for mpox exposure or anticipate potential exposure to mpox per the CDC (BII), including those who request vaccination (CII)	Administer two-dose series of JYNNEOS (0.5 mL SQ [preferred] or 0.1 mL ID [alternative]) given 28 days apart (AII). Administration of live-replicating vaccinia vaccines (i.e., ACAM2000) to people with HIV is contraindicated (AII).	JYNNEOS can be coadministered with most other vaccines. Adolescent and young adult men might consider a 4-week interval between receiving JYNNEOS vaccine and a COVID-19 vaccine because of potential risk for myocarditis and pericarditis. JYNNEOS can be administered to people who are pregnant, breastfeeding, or trying to become pregnant and those who require vaccination (BIII).	No difference in recommendations
	Post-exposure prophylaxis	For unvaccinated people with HIV who experience a known or presumed exposure, administer complete series (two doses 0 and 4 weeks [28 days]) of JYNNEOS, with the first dose given as soon as possible within 4 to 14 days after exposure to mpox (BII).	JYNNEOS can be administered to people who are pregnant, breastfeeding, or trying to become pregnant and those who require post-exposure prophylaxis (BIII).	
Pneumococcal	No prior pneumococcal vaccine or unknown vaccination history	Administer either of the following: • PCV20 (Prevnar20): 0.5 mL IM x 1 (AII); or • PCV15 (Vaxneuvance): 0.5 mL IM × 1 followed at least 8 weeks later by PPSV23 (Pneumovax) 0.5 mL IM × 1 (AII).	Although people with HIV with CD4 count <200 cells/mm^3 can be offered PPSV23 at least 8 weeks after receiving PCV15 (CIII) (such as if there are concerns with retention in care), PPSV23 should preferably be deferred until after an individual's CD4 count increases to >200 cells/mm^3 while on ART (BIII).	In June 2024, ACIP recommended PCV21 as an option for adults aged ≥19 years who are currently recommended to receive PCV15 or PCV20. Data and recommendations for PCV21 are currently under review in the

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations

	Previously received PCV13 and PPSV23	If <65 years when received dose of PPSV23:
		
		 • Administer PCV20 0.5 mL IM x 1 at least 5 years after the last pneumococcal vaccine (CIII); or
		
		 • Revaccinate the following with PPSV23 0.5 mL IM x 1 (BIII):
		
		  o Adults aged 19–64 years if ≥5 years since the first PPSV23 dose
		
		  o Adults aged ≥65 years if—
		
		    ▪ Previous PPSV23 administered at age <65, and
		
		    ▪ ≥5 years since the previous PPSV23 dose, and
		
		    ▪ At least 8 weeks after receipt of PCV13
		
		 If ≥65 years when received dose of PPSV23:
		
		 • No further doses of PPSV23 are required.
		
		 • Shared decision-making is recommended regarding administration of PCV20 for adults aged ≥65 years who have completed both PCV13 and PPSV23.
		
		 If PCV20 given, administer at least 5 years after last pneumococcal vaccine dose (CIII).
			Patients should receive a maximum of three doses of PPSV23. There is no need to give additional doses of PPSV23 every 5 years.	Adult and Adolescent Opportunistic Infection Guidelines.

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Previously received only PCV13	Administer PCV20 0.5 mL IM x 1 at least 1 year after PCV13 (BIII); *or* Administer initial dose of PPSV23 0.5 mL IM × 1 at least 8 weeks after PCV13 (AII). Revaccinate the following patients with PPSV23 0.5 mL IM x 1 (BIII): • Adults aged 19–64 years if ≥5 years since the first PPSV23 dose • Adults aged ≥65 years if ≥5 years since the previous PPSV23 dose	In patients who received PCV13 when their CD4 count was <200 cells/mm^3 and in whom PPSV23 will be given, some experts may choose to defer PPSV23 until CD4 count is >200 cells/mm^3 to optimize vaccine efficacy (CIII).	
	Previously received only PPSV23	Administer either of the following at least 1 year after last PPSV23 dose: • PCV20: 0.5 mL IM x 1 (BIII); *or* • PCV15: 0.5 mL IM x 1 (BIII)	When PCV15 or PCV20 is used in people with history of PPSV23 receipt, follow up with another dose of PPSV23 is not necessary.	
Respiratory Syncytial Virus (RSV)	Age ≥75 years	One dose 0.5 mL IM of RSV vaccine (Arexvy, Abrysvo, or mRESVIA) (CIII)	Limited data on efficacy and safety for people with HIV.	No difference in recommendations
	Age 60–74 years with a comorbid condition increasing the risk for severe RSV disease	One dose 0.5 mL IM of RSV vaccine (Arexvy, Abrysvo, or mRESVIA) (CIII)	Individuals ages 60–74 years with CD4 <200 cells/mm^3 are eligible, but limited data on immune response exist. Some clinicians may elect to wait for immune reconstitution prior to vaccination (CIII).	
	Pregnant people between 32–36 weeks' gestation	One dose 0.5 mL IM of RSV vaccine (Abrysvo) (CIII)	Limited data on efficacy and safety for people with HIV	

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
			Seasonal administration recommended. **RSV season in the continental United** States is typically September–January but differs by year and geography. Ideally, should be given at least 14 days prior to delivery	
Tetanus, Diphtheria, and Pertussis	Not previously vaccinated	One dose 0.5 mL IM Tdap (Adacel or Boostrix), followed by one dose of Td or Tdap at least 4 weeks after Tdap and another dose of Td or Tdap 6 months to 12 months later, then give Td or Tdap every 10 years **(AII)**	Tdap can be substituted for any Td dose and is always preferred as the first dose.	No difference in recommendations
	Did not receive Tdap at age 11 years or older	One dose 0.5 mL IM Tdap (Adacel or Boostrix), then Td or Tdap every 10 years **(AII)**	If indicated, give Tdap regardless of when the last dose of Td was given.	
	Pregnancy	Give Tdap preferably in early part of gestational weeks 27–36 **(AIII)**. One dose of Tdap is indicated for each pregnancy.	Give Td or Tdap booster every 10 years after Tdap.	
Varicella (Chickenpox)	CD4 count ≥200 cells/mm^3 with no evidence of immunity to varicella	Two-dose (0.5 mL SQ) series of VAR 4–8 weeks apart **(BIII)** Varivax **is contraindicated** if CD4 count <200 cells/mm^3 **(AIII)**. Varivax **is not recommended** in pregnancy **(AIII)**.	Evidence of immunity to varicella: • Documented receipt of two doses of Varivax or MMRV; *or* • Diagnosis of varicella or zoster by a health care provider; *or* • Laboratory evidence of immunity or disease	No difference in recommendations

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
			If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended **(AIII)**.	
Zoster	Age ≥18 years, regardless of a past episode of herpes zoster or receipt of attenuated ZVL (Zostavax)	Two-dose (0.5 mL IM) series of RZV (Shingrix) IM 2–6 months apart **(AIII)**. RZV **is not recommended** in pregnancy **(AIII)**.	To maximize immunologic response to the vaccine, consider delaying vaccination until patient is virologically suppressed on ART **(CIII)** or wait for immune reconstitution in those who had a CD4 count <200 cells/mm^3 **(CIII)**. Do not give RZV (Shingrix) during an acute episode of herpes zoster **(AIII)**.	ACIP recommends RZV for adults ≥19 years who are or will be at risk for herpes zoster. (This difference in age selected by ACIP was made to align with the age range in the adult immunization schedule.)

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Immunizations for Travel				
Cholera	Not routinely recommended for most travelers (CIII). Age 18–64 years with CD4 count >200 cells/mm^3 and traveling to an area where cholera has been epidemic or endemic within the past year	Lyophilized CVD 103-HgR (Vaxchora) single oral dose at least 10 days prior to potential exposure (CIII)	Safety and efficacy have not been established in people with HIV. No adverse effects reported with older formulation of vaccine in people with HIV without an AIDS diagnosis.	No current recommendations for people with HIV
Typhoid	At risk of *Salmonella* serotype Typhi infection (e.g., through travel, intimate exposure to a chronic carrier, occupational exposure) Revaccination only if continued or renewed exposure to *Salmonella* serotype Typhi is expected.	One dose 0.5 mL (25 mcg) IM Vi capsular polysaccharide vaccine (Typhim Vi) via IM injection at least 1 week before exposure (AIII) Revaccinate every 2 years if risk remains (BIII). The live attenuated oral typhoid vaccine (Vivotif) **is contraindicated** in people with HIV (AIII).	Provide education on other preventive measures against foodborne illness in addition to typhoid vaccination (AIII). Safety of typhoid vaccination in pregnancy is unknown. Consider avoiding during pregnancy or, if necessary, give Vi capsular polysaccharide vaccine (AIII).	ACIP has no position on the use of typhoid vaccine in people with HIV except not to give immunocompromised people the oral live attenuated typhoid vaccine.
Yellow Fever (YF)	**Age ≤59 years and at risk for YF virus acquisition** (e.g., by traveling to or living in areas at risk based on season, location, activities, and duration)	If indicated, provide vaccination at least 10 days prior to expected exposure. Age <59 years and asymptomatic with CD4 count >500 cells/mm^3: One dose of YF vaccine; revaccinate in >10 years if risk remains (BIII).	Provide vaccination as an adjunct to other protective measures against mosquito bites. **Pregnancy and age ≥60 years may** increase risk of complications from YF vaccine administration.	No difference in recommendations

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

		Any age and asymptomatic with CD4 count 200–499 cells/mm^3: YF vaccine may be considered depending on risk (**BIII**). YF vaccine **is contraindicated** for people with CD4 count <200 cells/mm^3. This recommendation is based on a theoretic increased risk for encephalitis in this population (**AII**).	If international travel requirements rather than an increased risk for acquiring YF infection are the only reason to vaccinate people with HIV, excuse the person from vaccination and issue a medical waiver to fulfill health regulations. Closely monitor people with HIV who have received YF vaccine for evidence of adverse events.	
Polio	Not routinely recommended (**AIII**)			No difference in recommendations
	Those at higher risk for exposure to poliovirus— such as those traveling to countries where polio is endemic—can be vaccinated with inactivated polio vaccine (IPV) (**CIII**).	Three doses IPV 0.5 ml IM at 0 and 1–2 months, with third dose given 6–12 months after second dose (**CIII**)		
	Previously vaccinated with one to two doses of vaccine	Give remaining doses of vaccine at recommended intervals (**CIII**)		

Key: ACIP = Advisory Committee on Immunization Practices; anti-HAV = hepatitis A virus antibody; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; HAV = hepatitis A virus; HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; HPV = human papillomavirus; ID = intradermal; IG = immunoglobulin; IgG = immunoglobulin G; IgM = immunoglobulin M; IIV = inactivated influenza vaccine; IM = intramuscular; IPV = inactivated polio vaccine; LAIV = live attenuated influenza vaccine; MenACWY = meningococcus serogroup A, C, W, Y; MenB = serogroup B meningococcal vaccination; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PCV21 = 21-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; RIV = recombinant influenza vaccine; RSV = respiratory syncytial virus; RZV = recombinant zoster vaccine; SQ = subcutaneous; Td = tetanus and diphtheria toxoids vaccine; Tdap = combination tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; VAR = varicella vaccine; YF = yellow fever; ZVL = zoster vaccine live

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Recommended Immunization Schedule for Adults and Adolescents With HIV

Vaccine	All People With HIV	Where Varies by Age	Where Varies by Pregnancy Status	Where Varies by CD4 Cell Count (cells/mm^3)	
				<200	≥200
COVID-19	For current COVID-19 vaccination recommendations, please visit the CDC's COVID-19 Vaccines website.			Recommendations differ with advanced or untreated HIV infection	
Hepatitis A (HepA, HepA-HepB)	Two to three doses (varies by formulation)				
Hepatitis B (HepBCpG, HepB, HepA-HepB)	Two to three doses (varies by formulation and indication)				
Human Papillomavirus (HPV)		Three doses for ages 18–26 years Consider for ages 27–45 years with shared decision-making	Not recommended during pregnancy		
Influenza (Multiple Vaccines)	One dose annually				
Measles, Mumps, Rubella (MMR)			Not recommended in pregnancy	Contraindicated	Two doses if born after 1956 and no history of vaccination or positive antibody titer
Meningococcal A,C,W,Y Conjugate (MenACWY)	Two doses, then booster every 5 years				
Meningococcal B (MenB)	Two to three doses (varies by formulation)		Not recommended during pregnancy		
Mpox (MVA-BN, Attenuated)	Two doses				
Mpox (ACAM2000, Live-Replicating)	Contraindicated		Not recommended during pregnancy		
Pneumococcal Conjugate (PCV15, PCV20)	One dose				
Pneumococcal Polysaccharide (PPSV23)	One dose (if conjugate vaccine was PCV-15)				
Respiratory Syncytial Virus (RSV)		One dose for people ages ≥75 years or those ages 60–74 years with a comorbid condition that increases risk for severe RSV disease	One dose for pregnant people between 32 and 36 weeks' gestation		
Tetanus, Diphtheria, Pertussis (Tdap/Td)	Tdap once, then Td or Tdap booster every 10 years		Recommend booster with each pregnancy		
Varicella (VAR)			Not recommended in pregnancy	Contraindicated	Two doses
Zoster Recombinant (RZV)		Two doses for people aged ≥18 years	Not recommended in pregnancy		

Legend:

Recommended for all adults and adolescents with HIV who meet the age requirement or lack documentation of vaccination or evidence of past infection.

Recommended for adults and adolescents with HIV with another risk factor (medical, occupational, or other indication) or in select circumstances.

Contraindicated

Note: Recommendations may differ from the Advisory Committee on Immunization Practices.

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