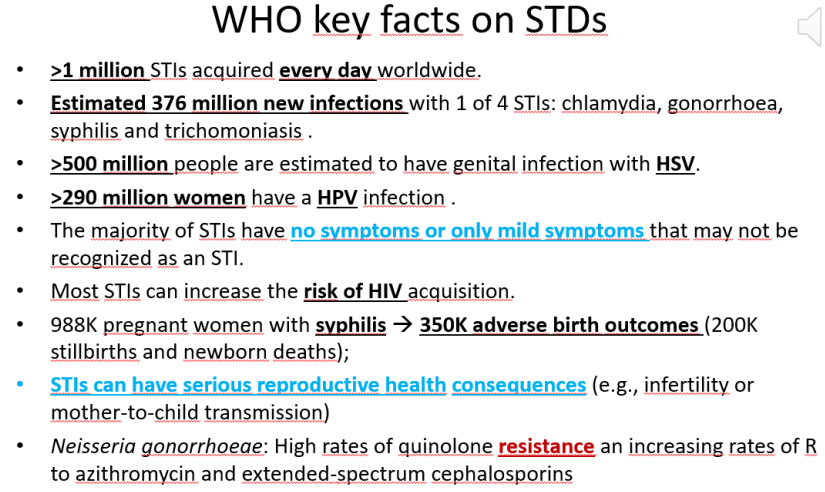
STD

Sexually Transmitted Infections (STIs), also known as Sexually Transmitted Diseases (STDs). They are quite common and more common than everyone can expect because in the general population's mind things like syphilis and gonorrhea are something from the 19th century, but they are still really common and in certain settings they cause epidemics. The epidemiology and the clinical impact of STDs will be explained and then few of these STDs will be discussed in order for you to get a basic knowledge of these diseases.

EPIDEMIOLOGY

Fig. 30



Referring to *Fig. 30*, the professor used some key facts on STDs from the WHO site in order to provide us with some numbers. Some of these numbers are unbelievable: everyday it is estimated that more than 1 million people will get an STD. All the other numbers are really high: for example, more than 500 million people have genital infections with *Herpes*, more than 300 million people have an *HPV* infection, although nowadays vaccination can change this number, for some other diseases it can't. For example, vaccine for *HPV* is not available in certain countries.

The majority of STIs have no symptoms or only mild symptoms and therefore people are not seeking medical help and they are not treated for the disease. What is very relevant for *HIV* is that most STIs can significantly increase the risk of *HIV* acquisition and transmission and that most of these STIs can affect reproductive health. Syphilis during pregnancy will lead to several consequences for the newborn but also *Chlamydia* infections can cause infertility and may be transmitted to the newborns. Resistance to antibiotics is a concern in several areas starting from Southeast Asia and USA and is globally spreading, causing trouble in treating these infections.

In several papers there is a distinction between curable and non-curable STDs:

- Non curable STDs include HIV, HSV, HPV (most of the viral infections);
- Curable STDs are Gonorrhea, Chlamydia, Syphilis and Trichomoniasis.

In this map *Fig. 31* taken from 2012 review, in which incidence of curable STIs is divided per different regions, there are areas in which incidence of chlamydia is very high: it can be as high as 60.9 cases per 1000 inhabitants. In the American region, chlamydia is high but also trichomoniasis is high (27.4 cases out of thousand individuals), almost as in the African region, where it is even higher (37.4 cases out of thousand). There are some geographical variations but in most of the tropical areas the incidence is higher.

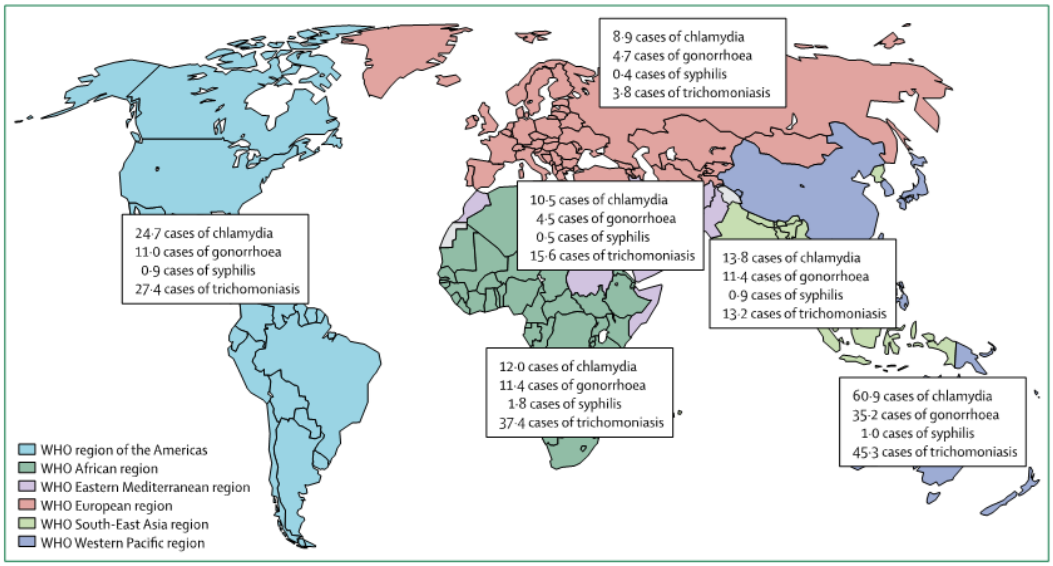


Figure 23

Fig. 31

Fig. 32

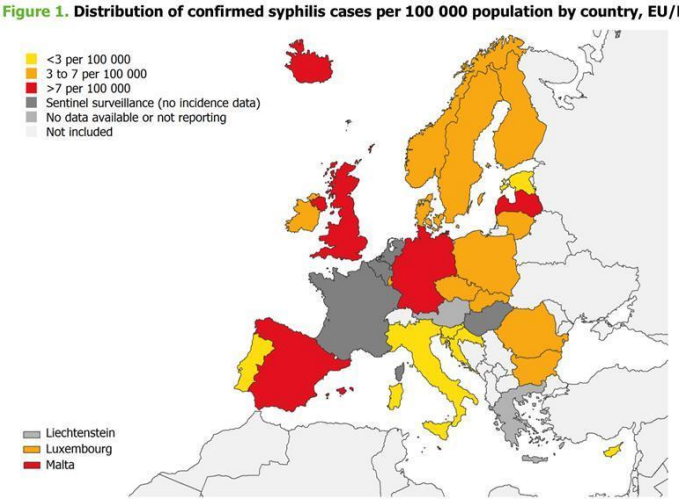


Fig. 32 is taken from the ECDC website1 to give an idea of the distribution and of the confirmed syphilis cases per 100,000 population by country. You can see that certain countries have no surveillance data, such as France and some countries in the middle of Europe (e.g. Liechtenstein) but other countries that are actually active reporting cases of syphilis, mainly Spain, UK, Germany and some of the Baltic Republics, have a significantly high incidence above 7 cases per 100,000 inhabitants.
In Italy, it seems to be low, but the professor thinks that there is a very high underreporting of cases due to the fact that syphilis must be suspected (often it is not) in order to be diagnosed and reported.

SYPHILIS TRENDS

These are the trends in the last 10 years showing a mild reduction in STDs among heterosexual individuals[2] but a steep increase in all STIs in MSM (Men having Sex with Men)*Fig. 33*. Both in EU and in UK there is a constant increase in the number of infections reported, having MSM as a prevalent risk factor.

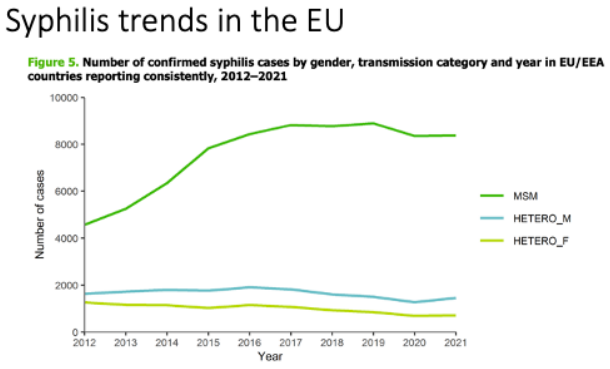


Fig. 33

Fig. 34 is about MSM in the UK. The blue line indicates HIV infection which increased from 1996, then there was a plateau and from 2014 only it is slightly decreasing due to the events pointed at by the black arrows. Look at Early syphilis in red, Gonorrhoea in green and Chlamydia in purple: you can see that all of them have markedly increased their incidence over time in recent years.
Here *Fig. 35* there is a report of the STDs in Piedmont published in 2018, that refers to data collected in 2016. Gonorrhoea increased in the last 10 years, especially in men; syphilis is pretty stable (because of a decrease in women and an increase in men);

Lymphogranuloma venereum (LGV) cases are mostly from 2009, due to the fact that before this date we didn't have the specific PCR for *Chlamydia trachomatis* so we weren't able to diagnose it. The dark orange shows LGV patients that were already known as HIV+ and some, who were diagnosed at the same time, were HIV- (just a minor group of LGV cases - *look at column 2010, ed*).

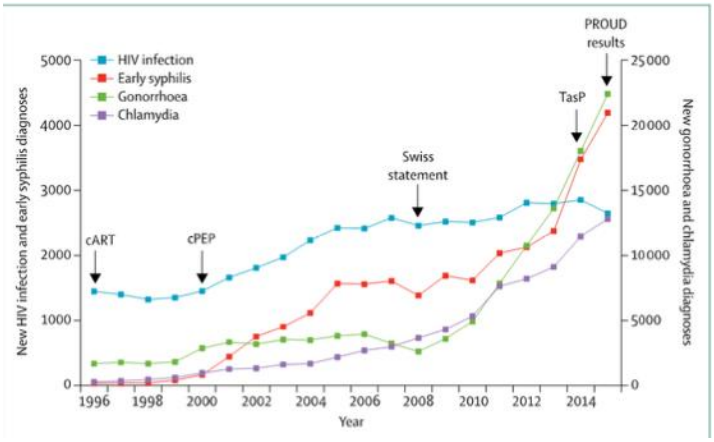
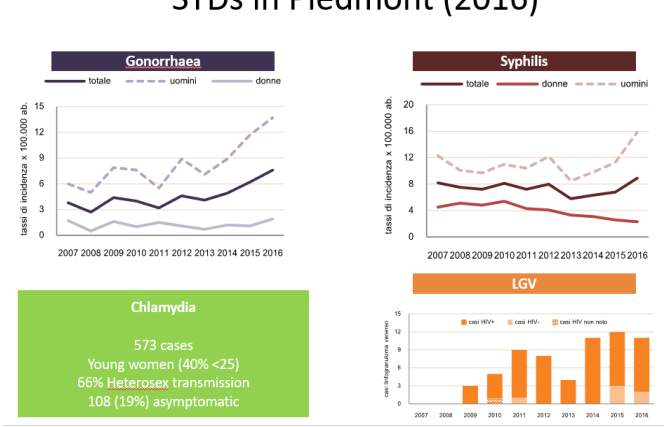


Fig. 34

For chlamydia, in 2016 we found more than 500 cases, mostly young women and a lot of heterosexual transmission and 1/5 of cases were completely asymptomatic (chlamydia was just discovered as a part of the global screening).

Fig. 35

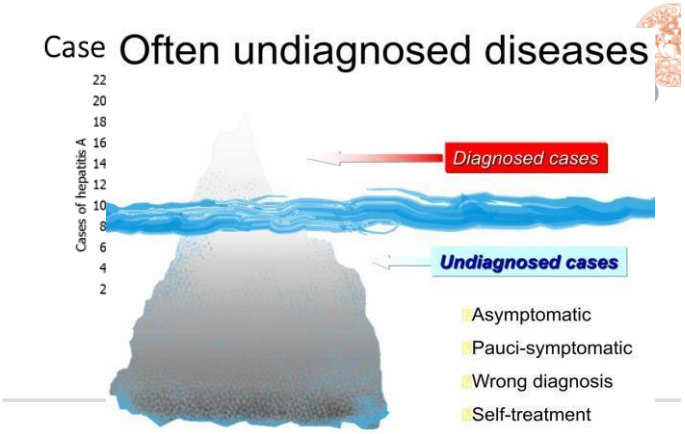


CASES OF ACUTE HEPATITIS A

A table summarizing all the infections which can be transmitted by sexual intercourse will be shown later; in the meantime, bear in mind that *HAV* is one of those. We thought that *HAV* was only a foodborne infection but the habit of rimming i.e. the oral to anal intercourse, the so-called blackies[3], increased a lot mostly in groups such as MSM and that is why we had such a steep increase in 2017-'18-'19 in Hepatitis A among young MSM. That is why we suggest vaccination for *HAV* in those patients. STIs cases can be represented as an iceberg in which the diagnosed cases are only the visible part i.e. the tip.

Diagnosed cases account for 10-20% of the real cases: the real STI numbers seem to be much higher because most of the cases are asymptomatic or paucisymptomatic, some of them are treated for a wrong diagnosis and others with self-treatment (that can actually decrease the number) e.g. if you think you have an STD, you go to your doctor but you don't want to tell him you have an STI, so you might say you have sore throat and fever and he will give you an antibiotic treatment which might decrease the symptoms, but hamper the evolution of the STI.

Fig. 36



COMORBIDITIES

The risk of acquiring HIV infection due to concomitant STDs increases exponentially. For some STDs it is pretty clear due to the presence of ulcerations: there is

damage in the mucosa, so there might be *HIV* transmission. Some diseases as gonorrhoea and chlamydia don't directly present lesions on the mucosa but show inflammation which can be a route of HIV transmission: in this state there are a lot of white blood cells which can be either receptive for *HIV* and cause infection or can harbor *HIV* inside them and pass *HIV* to the partner.

STDs and the risk of acquiring HIV

- STDs increase the risk of acquiring and transmitting HIV
  - Early diagnosis and treatment→ improved prevention of HIV
- Risk of acquiring HIV:
  - Condylomas R.R. 6
  - Urethritis R.R. 5.8
  - Gonorrhoea R.R. 4.8
  - Chlamydia R.R 3.6
  - Trichomonas R.R 1.9

STDs Complications

The majority of STDs complications are in women: most STDs are asymptomatic only in women and for this reason they are not diagnosed and treated. For example, chlamydia is mildly symptomatic in men, but it is absolutely asymptomatic in women.
In general STDs in women can cause infertility, chronic abdominal pain and pelvic inflammatory disease. During pregnancy, an STD can cause abortions, extrauterine pregnancy, newborn prematurity and infections, not only if it was contract right before pregnancy but also a few years before because of the chronic inflammatory modifications that occurred. Some STDs can have very serious complications, e.g. *HPV* is associated with cervical and anal cancer.

What should be the features of an STDs clinic?

Until last year we had two different STD clinics in Turin: the Savoia hospital and the San Lazzaro dermatological hospital. Today we have a single STD clinic and the clinics should have some of these features:

- Convenient opening hours[4]: opening hours should be flexible and available in order to allow certain populations to use the service;
- Ask about the past medical history, sexual preference and risky behavior[5]: it is very important to ask the questions in a delicate and appropriate way and never be judgmental, otherwise we will not get the answers and we will not understand the risky behaviors;
- Examinations should be performed including vaginal examination and withdrawing samples (some internal and some external);
- Rapid smear (fresh and gram staining) is often enough to obtain the diagnosis. For example, fresh stain of *Trichomonas (vaginalis, ed)* and the fresh smear of *(Neisseria, ed) gonorrhea* or other bacteria and fungi are all successfully diagnostic;
- Provide an immediate treatment either on the base of the smear or in presumptive way[6] in order to reduce the risk of transmission during the following days;
- Suggest partner notification and treatment in some STDs[7];
- The service must include counselling, prevention and follow up. In some diseases such as *HIV* also pre-exposure prophylaxis is fundamental.

Fig. 37

BACTERIA	VIRUSES	FUNGI	PROTOZOA
Chlamydia trachomatis→ aspecific urethritis and Lymphogranuloma venereum (LGV)	***HPV*** → Condilomas ***HPV*** → Carcinomas		***Trichomonas vaginalis*** → Trichomoniasis
Neisseria gonhorroeae → gonhorrea	***HSV2 (HSV1)*** → Herpes genitalis		
Treponema pallidum → syphilis	***HIV*** → AIDS		
Haemophylus ducrey → chancroid	***HBV*** → Hepatitis B		
Calymmatobacterium granulomatis/genitalium, Gardnerella vaginalis, Mycoplasma/Ureaplasma	*HAV, HCV*	*Candida?*	**ECTOPARASSITES** ***Sarcoptes scabiei, Phtirus pubis***

Aetiologies
Here is a table trying to summarize bacteria, viruses, fungi, protozoa and ectoparasites that can cause STIs.

- ●Bacteria:*trachomatis Chlamydia* especially and urethritis

Lymphogranuloma LGV), *gonorrhoeae*, *pallidum* venereum, *Neisseria Treponema* (agent of syphilis) and *Haemophilus ducreyi* (agent of chancroid). There are other bacteria causing vaginitis (e.g. *Gardnerella vaginalis*). There are two *Mycoplasma/Ureaplasma* that usually are asymptomatic in the genital tract but may cause urinary inflammation;

- Viruses: *HPV*, we know that can cause both condylomas, carcinomas and cancer. *HSV2* will cause herpes genitalis, *HIV* will cause AIDS, *HBV* Hepatitis B, *HAC*, *HCV*[8];
- Fungi: we will see *Candida* even though the professor says it is hardly transmittable in the majority of subjects;
- Protozoa: *Trichomonas vaginalis* - trichomoniasis;
- Ectoparasites: *Sarcoptes scabiei* and *Phthirus pubis*.

SEXUALLY TRANSMITTED INFECTIONS (STIS)/DISEASES (STDS)

GONORRHOEA- NEISSERIA GONORRHOEAE

Neisseria gonorrhea is a gram-negative diplococcus, very fragile in external environment. To grow in culture it needs specific means, it should be heated at 37° and kept in the heater, then examined and sent as soon as possible to the lab to preserve the culture.

- Incubation time is short, around few days (2-7);
- Signs and symptoms: it is associated with purulent urethritis, cervicitis and proctitis which are characterized by whitish and yellowish secretions with pruritus and pain (for this reason patients usually seek medical advice);
- Diagnosis is usually made with culture on urethral (PCR) and cervical swab;
- Treatment: straightforward, usually ceftriaxone at very low dose (250mg) or ciprofloxacin single dose - up to 1 gram. This can be done at alternative regimen although nowadays there are increasing rates of resistance to ATB[1] including fluoroquinolones, azithromycin, and ceftriaxone, all over the world but especially in the US and in Southeast Asia.
- It is important not only to trat the patient but to enforce the importance of notify the partner.

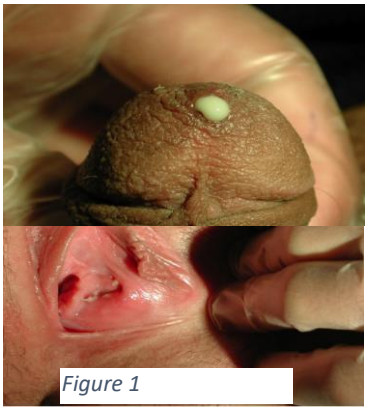


Figure 1

REITER'S SYNDROME

Also called **reactive arthritis**, mostly affecting large joints (especially lower limbs and knees) and it is asymmetrical. It might be associated with conjunctivitis and urethritis (sometimes gastroenteritis). It is associated with HLAB27+ genotype and it may present a few weeks after a gonococcal urethritis, but it is also associated with other bacteria, mainly gram-negative bacteria e.g. *Shigella* and *Yersinia* or *Chlamydia* as well.

CHLAMYDIA TRACHOMATIS

It is an obligate intracellular very small pathogen and there are different serovars divided in 3 classes:
A, B, C: causing trachoma, a conjunctivitis which can lead to blindness;
C to K: aspecific urethritis (e.g. cervicitis, salpingitis, proctitis), in women PID i.e. pelvic inflammatory disease, and potentially infertility;
L1 to L3: associated with Lymphogranuloma venereum, LGV.
Diagnosis: PCR for *Chlamydia* DNA in urines; also a swab can be used but it is much easier to do it in urine.
Treatment is azithromycin 1gr single dose (doxycycline can also be used). The combination of ceftriaxone and azithromycin will cure both *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.
Signs: **aspecific urethritis**, secretions, pruritus and pain when urinating.
Male will usually seek medical advice while females will not as it is mostly asymptomatic in females, which is why usually transmission is mediated by woman.
Complication: **Lymphogranuloma venereum** is associated with L1-L3 serovars of *Chlamydia trachomatis* with an incubation period of 5-21 days. It is more common in tropical countries. It has 3 phases:

Aspecific urethritis

Figure 2

LGV inguinal lymphadenitis

Figure 3

[1] antibodies

1. Chancroid, a non-painful ulcer, usually there is an inoculum of *Chlamydia* (remember: non-painful ulcers in genital area can be either LGV or syphilis);
2. After few days: painful satellite lymphadenitis with systemic symptoms (e.g. low-grade fever and malaise);
3. Chronic phase: acute proctitis/colitis with mucous purulent loss from anus, bloody stools, tenesmus, fever and pain. It is a hard DDX with IBDs due to similar signs and symptoms e.g. a lot of patients affected by LGV are wrongly diagnosed with RCU[2].

3. SYPHILIS - TREPONEMA PALLIDUM

It is not very easy to diagnose syphilis unless there are very clear signs and symptoms. The agent of syphilis is *Treponema pallidum* which is a motile gram-negative Spirochaeta.
The disease has 3 well-defined stages:

1. **Primary syphilis** (where the inoculum is) is characterized by non-painful ulcers in the genital, sometime oral, areas. Typically, the genital ones affect penis and vagina, while the oral ulcers can be harder to detect. Anal ulcers are usually almost impossible to detect since they are not painful;
2. **Secondary syphilis**: it usually occurs 4-10 weeks after primary syphilis and is characterized by fever, malaise, there is an interesting rough maculopapular rash, non-confluent and non-itchy. It is reddish-brown (rusty color) and involves the palms of the hands and the bottom of the feet[3]. This rash is very typical as it is one of the few rashes involving these parts of the body, so if you see them, think of syphilis and don't touch these rashes as they are very contagious (as they are full of *Treponema*)[4];

Figure 4

3. **Tertiary syphilis:** usually occurs if antibiotic treatment was not used in the previous phases, it occurs 10-15 years after the first infection. It is less common as antibiotics are more and more used in rich-resource countries. It occurs many years after infection and is characterized by granulomas (so called ***"syphilitic gummas"***) that can be detected in several organs (CNS, liver, aorta and several others). It may take between 10 to 30 years to develop from infection without any treatment due to the fact that antibiotic treatment somehow reduces the *Treponema* replication and the body reaction *to inflammation (ed)*, consisting in the development of granulomas in the body tissues.

Figure 5

STAGES AND TIME FRAMES OF SYPHILIS

[2] NdR2: RCU is the acronym in Italian for Rettocolite Ulcerosa, in English Ulcerative Colitis.
[3] "you should remember it!"
[4] Quote: "and I don't think it's a funny way to get syphilis"

Primary	Chancre, regional lymphadenopathy	3 wk (3–90 days)
Secondary	Rash, fever, malaise, lymphadenopathy, mucus lesions, condyloma lata, alopecia, meningitis, headaches	2–12 wk (2 wk–6 mos)
Latent	Asymptomatic	Early, <1 yr; late, >1 yr
Tertiary		
Cardiovascular syphilis	Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis	10–30 yr
Neurosyphilis		
Asymptomatic	None	
Acute syphilitic meningitis	Headache, meningeal irritation, confusion	<2 yr
Meningovascular	Cranial nerve palsies	
General paresis	Prodrome: headache, vertigo, personality disturbances, followed by acute vascular event with focal findings	5–7 yr
Tabes dorsalis	Insidious onset of dementia associated with delusional state, fatigue, intention tremors, loss of facial-muscle tone	10–20 yr
	Lightning pains, dysuria, ataxia, Argyll Robertson pupil, areflexia, loss of proprioception	15–20 yr
Gumma	Monocytic infiltrates with tissue destruction of any organ	1–46 yr (most cases 15 yr)

Figure 6

Complication: Neurosyphilis

It is thought to be the direct invasion of the CNS by *Treponema* but it is much more common in HIV+ patients and so when we find HIV+ patients with titer against *Treponema*, we treat them more aggressively by performing a lumbar puncture in order to rule out neurosyphilis.

It may have a very different clinical presentation: most of the patients will be asymptomatic, others can present with *aseptic meningitis*. Neurosyphilis is an important consequence that we should rule out when we see someone with aseptic meningitis.

However, the chronic forms are very common, including:

Meningovascular Syphilis (vascular problems of the brain);

General Paresis of Insane: it is a kind of paralytic dementia that mostly presents with psychiatric symptoms;

Tabe Dorsalis: characterized by nerve root pain, sensory ataxia and often ocular involvement.

These complications are very rare (the professor never saw Tabe Dorsalis in his life, he only saw two or three cases of General Paresis) but it is important to know them and think of these complications in case of some dementia especially if you work in a psychiatric ward or in a neurologic ward. Be aware of these possibilities and eventually test for syphilis.

Diagnosis:

To diagnose syphilis, the usual screening test is **Treponema immunoglobulin (IgG)**, if it is positive, the laboratory usually will directly run a **Non Treponemal test** (**VDRL**)[5] and a **Treponemal test (TPHA)**[6]. With the combination of these three tests we are able to estimate the stage of infection.

VDRL tells us the activity of the disease, and the VDRL titer should be followed over time to see if the therapy is effective or if maybe patients have been reinfected (especially in cases of immunosuppression).

After treatment, some patients will show a decrease in VDRL, then after reinfection they will show a new increase in VDRL and, every time, they will be exposed to new complications.

If we have a primary or secondary syphilis, we can perform a test of direct evidence by swabbing lesions and analyzing them in dark field microscopy (not so many labs have this) or PCR i.e. detection of *Treponema* DNA on these lesions is one of the way of demonstrating the presence of *Treponema*. Mostly in primary syphilis the serology is not that useful while direct PCR test is.

[5] Venereal Disease Research Laboratory test
[6] Treponema pallidum Haemagglutination Assay

Treatment:

Usually **Benzatil-Penicillin**[7] (2.4 millions of units) administered intramuscularly: 1 dose for primary syphilis and 3 doses for secondary syphilis (in this case doses are one week apart). This treatment is very painful (patient won't like you) and for this reason we also inject Lidocaine to reduce the muscle pain. Alternatively, we can use Ceftriaxone or Doxycycline.
Bear in mind that in secondary syphilis there could be the **Jarisch-Herxheimer reaction** which is an allergy to penicillin, it is the massive destruction of *Treponema*, so when we have a secondary syphilis, before the administration of penicillin, we should give a test dose of Amoxicillin and see if patient develops rash, hypotension or malaise, which are the typical signs of Herxheimer reaction. We usually give lots of steroid and follow the patient to see the progression.

4. CHANCROID - HAEMOPHILUS DUCREYI

Figure 7

It is really common in tropical areas, but you might also see it in Europe, even though it is uncommon.
"Chancroid" is the US way of describing "Ulcera molle", which are ulcers in genital areas (fig.10).
The agent is *Haemophilus ducreyi* whose incubation period is 3-5 days. Vesicles open in a chancroid (soft painful ulceration with basal exudate), which is more similar to herpes.
N.B. remember painful ulcers in genital areas!
We rely on clinical diagnosis as the sore is very hard to turn positive even with an appropriate lab technique. Treatment is ceftriaxone or ciprofloxacin or azithromycin; the same treatment of *Neisseria gonorrhoeae* will work for this STI.

5. HERPES GENITALIS

Figure 8

It is usually associated with *HSV2* (some cases *HSV1*) and patients present with highly painful ulcerations in genital areas, preceded by pain and paresthesias, sometimes also dysuria, leukorrhea and itch in genital areas.
Clinical presentation is very similar to *HSV1* (*Herpes labialis*), just in different regions. It is often recurrent (in more than 80% cases): it can come back every month and last for 7-10 days, the quality of life will be highly affected as you will have excruciating pain for 10/30 days and you cannot have sexual intercourse because it is painful and there's risk of contagion. For this reason, it will be a cause of distress for several patients which will lead them to search for medical treatment.
Diagnosis: typically clinical, based on history and clinical presentation. There is also serological diagnosis, which is specific for *HSV2* and it could help to rule it out by assessing the presence of antibodies against *HSV2* or run PCR by swabbing on this ulceration and looking for *HSV2* and *HSV1* DNA.
Treatment: Acyclovir or Valacyclovir (in pills), in case of frequent recurrences we may use suppressive treatment for a few months (usually 6) to reduce relapses and improve the patient quality of life of the patient.

[7] "so it is Depo Penicillin"

6. TRICHOMONIASIS - TRICHOMONAS VAGINALIS

Agent of Trichomoniasis is *Trichomonas vaginalis* which is a very mobile protozoon, it has a short-medium incubation period 4-28 days.
It usually causes very few symptoms:
in females: vaginitis with itch, dysuria, leukorrhea, dyspareunia. The discharged are characterized by a fishy odor, so usually the smell is bad, which is one of the reasons why many patients seek medical advice;
in males: usually asymptomatic urethritis.
Diagnosis is made on fresh smear obtained by swabbing the vaginal fluid and looking at fresh staining under the microscope. Under the microscope we can recognize the moving *Trichomonas* (fig.7).
Diagnosis can be also clinical due to the presence of liquid leukorrhea with typical fishy odor, but it has to be followed by smear examination. Also PCR can be done after collecting urine[8].


Figure 9

Treatment: Metronidazole 2 gr single dose (normally a combination of pills in a single dose) to the patient and his/her partner. During this period alcohol should be avoided as it will interfere with metronidazole giving GI reactions.
Incidence of *Trichomonas vaginalis* (*infection, ed*) is raising over time.
The *Trichomonas vaginalis* is visible under microscope: the fresh smear with the protozoa moving around can be seen.

7. GENITAL CANDIDIASIS

Candida is a commensal yeast which can be found in the skin, mouth, gut, vaginal flora. However, there are some predisposing conditions in which *Candida* will overgrow: diabetes, immune depression, microbiota alterations with reduced *lactobacilli* (antibiotics, mucositis, altered pH). It can be potentially transmittable, but it is very uncommon; in fact, when you analyze genetic strains in partners, 99% of the time the strains are different (only specific for the partner). Just a minority is found to be transmittable. We don't believe it is a contagious disease and for this reason we don't treat the partner in case of vaginal candidiasis.
Clinical presentation: itchy vulvovaginitis with whitish leukorrhea ("cottage cheese") due to the fact that it is more firm compared to *Trichomonas* (the aspect is cheesy). It can cause balanoposthitis with erythematous papules in men, but it is very uncommon as usually men don't have symptoms at all.
Diagnosis is mostly clinical. We might also perform an exudate culture, usually in patients that have recurrences, in order to rule out a resistance to fluconazole, which is one of the most used antifungal agents in this setting.

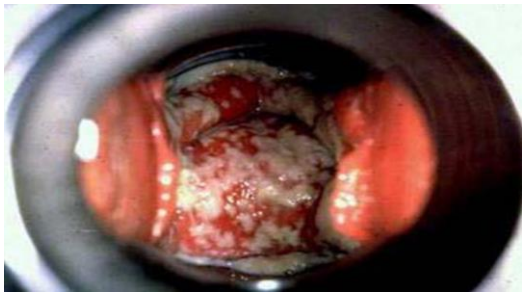


Figure 10

Treatment is usually local with ovules (clotrimazole, miconazole) or oral in severe cases (fluconazole, itraconazole). In case of frequent recurrences, suppressive therapy may be used to reduce the relapses which are usually associated with perimenstrual[9] period due to changes in pH and flora, for which *Candida* can

[8] Taken from slide 36 of 2019
[9] NdR2: He said "**premenopausal**"; however, I believe it should be **perimenstrual**. Indeed, hormonal fluctuations before the menstrual cycle can trigger changes in the bacteria in the vagina and high levels of estrogen cause *Candida* fungi to overgrow. Moreover, later he says "they have Candida in the days before menstruation".
NCBI: "daily colonization of Candida during the luteal phase of the menstrual cycle is described (...)

replicate faster and become the predominant species in vagina. Most of patients indeed will tell you that they have *Candida* in the days before menstruation.

8. CONDYLOMAS

HPV[10] causes Condylomata Acuminata, commonly known as genital warts.
Remember the difference with Condyloma Lata that are wart-like lesions caused by syphilis: secondary syphilis that instead of having a diffuse rash, presents with localized papules that look like condylomas but are syphilomas. Condylomas are most frequently associated with *HPV serotypes 6 and 11.* They can be external (genital areas, trunk) or internal condylomas.
Diagnosis is usually clinical.
Treatment[11] varies according to number of warts and their localization. It can be:
Removal (surgery, cryotherapy, cauterization);
Topical therapy (purified podophyllotoxin, imiquimod, sinecatechin) to reduce the dimension of the external warts and "make them fall off";
The vaccine specific for these serotypes could reduce the incidence of condylomas over time.

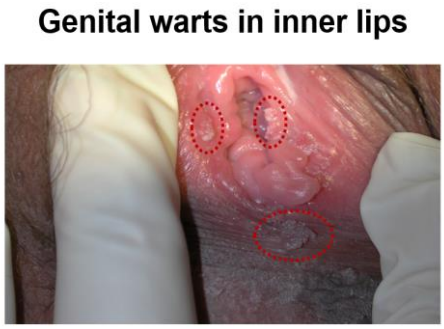


Figure 11

Figure 12

9. ECTOPARASITES

They are included in this lesson as they can be transmitted by sexual intercourse or by close contact with other people.

Some of these insects are:

- **Lice**: *Pediculus humanus* and *Phthirus pubis;*
- **Flies, Bedbugs and Fleas** are very common in certain areas. They normally don't directly cause diseases (even if potentially they can) but they can cause lesions that need to be differentiated from infectious lesions;
- **Mites** can cause diseases, especially *Sarcoptes scabiei* (the itch mite) which is the agent of scabies.

demonstrating an increase in the colony count preceding symptom development".
[10] will be discussed shortly since it will be a topic of both Oncology and Gynecology courses.
[11] it will probably be discussed also in the Dermatology course.

Insects		
1. Lice	*Pediculus humanus* (head or body louse)	Pruritus of scalp or trunk; nits (lendini) seen on hair shaft
	Phthirus pubis (pubic louse)	Pruritus in pubic area; nits seen on hair shaft
2. Flies	*Dermatobia hominis* (botfly)	Pruritic, painful, and erythematous nodule; larva may be seen emerging from nodule
3. Bedbugs	*Cimex lectularius* (common bedbug)	Pruritic, erythematous wheal (ponfo)
4. Fleas	*Pulex irritans* (house flea)	Pruritic, erythematous nodule
Arachnids		
1. Mites	*Sarcoptes scabiei* (itch mite)	Pruritic, erythematous papules, and linear tracks
2. Ticks	*Dermacentor species*	Ascending paralysis
3. Spiders	*Latrodectus mactans* (black widow spider)	Severe pain and muscle spasms
	Loxosceles reclusa (brown recluse spider)	Necrotic ulcer

Figure 13

9A. LICE

It is important for you to have an idea of the difference between head lice, body lice and pubic lice in terms of agents, symptoms. They can be visible as the adult insect or more commonly as nits (more visible than lice). Symptoms are similar and affect certain areas: they can cause discoloration of the skin, chronic itching, psychological problems but globally itch is the major symptom.

Figure 14

- Head lice: Pediculus humanus capitis (2-3 mm long)
- Body lice: Pediculus humanus humanus (2.3-3.6 mm long)
- Pubic lice (crabs): Phthirus pubis (1.1-1.8 mm long)[12]
Head lice found anywhere on the head (typically hair, but also can be found on the eyebrows).
Body lice: typically found on the clothing, except when they need a blood meal. They then move to the skin (but usually found on the clothing NOT the skin).
Pubic lice: usually found in pubic hair but are adapted to any other type of coarse hair (armpit region etc.)
All of the lice types are six-legged.
Differ on the basis of morphology (see pictures, especially pubic lice), where they can be found and size.

three types of lice[13]**:**

- They are ectoparasites, they live on the surface of the host, as opposed to inside the body (endoparasite) as with many other parasites we've seen. **Do** need blood meals to survive;
- Move by crawling, as opposed to flying or hopping, which affects the control and prevention measures needed;
- Feet are specifically adapted to human hair (cannot survive for that long if they fall off a human.) They can only live 1-2 days if they fall off of a human host;
- Have humans as their only host species, there is no animal reservoir, which makes control measures different and potentially simpler than other parasites;

[12] from slide 45
[13] Starting here until the end of paragraph "Epidemiology & risk factors" the information has been taken from the slides and notes professor made at the bottom.

- Have similar life cycles:
    - Egg/nit: usually located no more than 1/4 inches from the base of the human hair scalp. It's attached by a sticky glue-like substance secreted by the adult louse, which is what allows it to stick to the human hair. Takes 8-9 days to hatch;
    - Nymph (3 molts): There are three molting stages. Takes the nymphs approximately one week in total to move into the adult stage. The nymphs must take a blood meal in order to move on the next molting stage (therefore need three blood meals in total);
    - Adult: Can live up to 30 days on the human host. Die within 1-2 days without the human host. All adult lice need a blood meal in order to survive (nutrients). Females need it in particular for oviposition.

  Both nymphs and adults take blood meals from the human host.

Symptoms of HEAD and PUBIC lice:

- Itching: mostly due to the lice biting (people are somewhat allergic to the bite);
- Difficulty Sleeping: this is due to vector biology - the lice are more active at night, so biting and itching are more likely to occur at night;
- Sores and secondary bacterial infections from scratching: caused by scratching the itchy bites (and bacteria that's on the fingers or on the scalp can get into the bite). This is a minor symptom and isn't observed as often as the common itching!

Symptoms of BODY lice:

- Intense itching: more than head lice usually because there are more lice;
    - Skin discoloration/thickening: if infection is ongoing for a long period time (lots of lice bites), there can be skin discoloration and thickening in the areas with lots of bites.
    - Red rash appears where the lice have bitten;
    - Secondary bacterial infections from prolonged scratching: as with head lice, open wound → bacteria can enter from hands or surrounding skin area.

Diagnosis is based on direct visualization, i.e. observation of live nymphs or adult lice, made easier by using a fine-teeth comb and magnifying glass. Finding nits is suggestive of infection but not definitive.
Nits are very small, and it is difficult to correctly identify them. They are often mistaken for other things in the hair: dandruff, droplets of hairspray, etc.
Old nits can persist in the hair for a long time after infection (due to the sticky substance holding them to hair), so finding these old nits only indicates an old infection. Not necessarily an active infection that is still ongoing.
Lice are small, quick, and avoid the light (are most active at night).
In body lice, because lice are not normally found on the skin, you should look for them on the clothing. They can typically be found in the seams (along with nits)

EPIDEMIOLOGY & RISK FACTORS

- Head lice: “head-to-head transmission” since lice do not live very long without a human host and are not adapted to walking along smooth surfaces that do not have human hair. They are found worldwide, causes 6-12 million cases per year in the United States in children age 3-11. Typically occurs more often with children and in schools and is not associated with poor hygiene. Girls are at higher risk than boys, probably because of more social contact, playing with hair, etc. African American subjects are less affected than other groups because lice are specifically adapted to clinging the best to certain types of human hair;

- Pubic lice: worldwide prevalence estimated of 2%, it can spread through sexual contact and fomites (clothing, linens, towels belonging to an infected person. If found on children, pubic lice can be an indicator of sexual abuse;
- Body lice: associated with poor hygiene and crowded living conditions ex. prisons, homeless transient populations

Remember that body lice can transmit several bugs. Following a few "historical" examples:

- **Louse Borne Relapsing Fever** (caused by *Borrelia recurrentis*): there were several cases in migrants kept prisoners in Libya and through their journey to Italy. [14]*High case-fatality (10%) in WWII; mortality is 30-70% without treatment. It is more severe than the tick-borne version. Often found in epidemics amid poor-living conditions (and in war, like WWII) -- developing world. Spread when an uninfected human crushes an infected louse. B. recurrentis is spread via mucous membranes and then invades bloodstream. There is no animal reservoir and can alter the protein surface (causes relapses "relapsing fever"*);
- **Trench Fever** (caused by *Bartonella quintana*) during WWI. *It is rarely fatal with serious symptoms e.g. acute fever onset (five days), headache, myalgias, rashes, splenomegaly (less common)*;
- **Epidemic Typhus** (caused by *Rickettsia prowazekii*): *significant contributor to worldwide mortality (millions) before antibiotic treatment. It is classified as a category B bioterrorism agent (second most severe category) i.e. moderately easy to disseminate.*

If you find body lice, it is important to check also for these diseases, since some of these are being observed in certain areas of the world (limited resources-countries) in the setting of humanitarian problems and incarceration.

Lice Treatment[15]

- If only nits are visible (no nymphs or adult lice) probably the infection is not active and treatment may not be necessary, however it is suggested because lice nits are not easy to recognize. This treatment consist in **topical pediculicides** (there is resistance concern over the world): pyrethroids are the most used ones, in particular **permethrin at 1% concentration**, to be applied at day 0 and a second round 7-10 days, even 14, after;
- In case **body lice is present a higher (5%) concentration is preferred**, since the insect seems to be more resistant. A higher concentration is applied and left on for a few hours after application;
- **Oral ivermectin** is another option for lice in case topical treatments cannot be used. It was first used against onchocerciasis[16], but is also the drug of choice for strongyloidiasis[17] and is effective against scabies.

9B. SCABIES - SARCOPTES SCABIEI

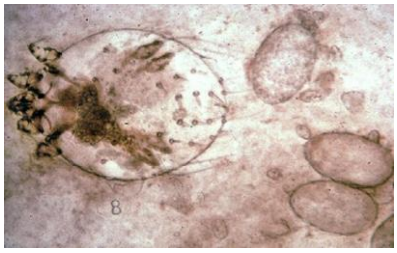


Figure 15

Prevalence of scabies is estimated to be high all over the world (at 100 million people), with however a high variability (0.2-71%), the highest rates are in limited resources settings and in Pacific and Latin American countries. It is also more common in crowded conditions, for example it can cause epidemics in long-term care facilities and prisons. Every time there is a case in the emergency room, panic breaks out. It's not really that highly contagious: you need to be in contact for some time with the skin of someone who has it to get

[14] Information in *italics* in this paragraph is taken from Professor's notes on powerpoint presentation

[15] "I think it is very common. Before losing my hair, when I was a child, I have been treated at least 5-6 times for hair lice" -cit

[16] From sbobinatore: Onchocerciasis, commonly known as "river blindness", is caused by the parasitic worm Onchocerca volvulus.

[17] From sbobinatore: Strongyloidiasis is a chronic parasitic infection of humans caused by Strongyloides stercoralis.

it. However, it can cause small epidemics and can be slightly contagious.
The pathogen is ***Sarcoptes scabiei***, an 8-legged mite. The females burrow into the epidermis after mating, and lay 2-3 eggs/day, but die after a few weeks. Larvae hatch in 3-4 days and as adults they can cause new rounds of infections and lesions. Usually there's a low parasitic burden, so 10-15 per host. However, in the crusted scabies, also called Norwegian scabies, that occurs in an immunosuppressed host, there can be millions of mites, and that's why it's more serious, harder to treat, and more contagious. The mites die if they're laid out of the body for a few hours: they need to be in contact with the host body for optimal temperature and nutrition.
Transmission is based on prolonged skin-to-skin contact, fomites are usually uncommon but important for crusted scabies and animals do not transmit the mites.

CLASSIC SCABIES

3-6 weeks after infestation, classic scabies begins. There's a severe pruritus everywhere on the body that worsens at night. There might also be an hypersensitivity reaction to mites, feces or eggs: patients might have not only the typical lesions caused by mites, but also an allergic reaction to mites' components throughout the body. The lesions are multiple, small, erythematous papules, often excoriated. You might see burrows, even if they are not easy to see. They are thin serpiginous lines of different colors and are diagnostically significant.
In these pictures you can see an inflammatory reaction (left) and a burrow (right)

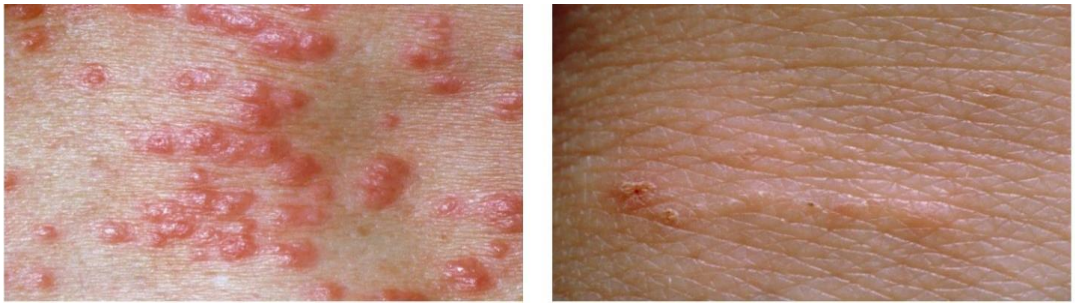


Figure 16

In fig.17, the most common places where you can find scabies lesions are in red, while the less common are in green, like the back and the head.

Remember to take a look between fingers and on the knees i.e. the two most common locations for scabies lesions.

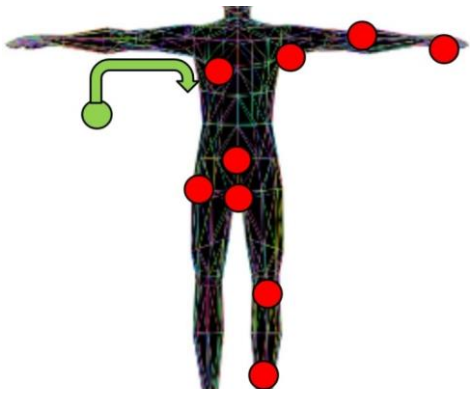


Figure 17

CRUSTED SCABIES (NORWEGIAN SCABIES)

It is the disease in immunosuppressed hosts, especially those with AIDS, lymphoma, or on chronic corticosteroids treatment. They have a very high mite burden, with less defined lesions resembling erythematous squamous patches that develop scales over them, as well as crusts, warts, fissures and they may smell badly because of underlying infection.
Complications: these lesions may complicate mostly with superinfections, usually from *staphylococci* or *streptococci*, that may cause impetigo, ecthyma, paronychia and furunculosis, potentially also

Figure 18

sepsis because of dissemination of gram-positive bacteria in all of the body through blood.
Diagnosis is usually clinical, according to presentation and risk factors. Skin scraping may help identifying mites at microscopical evaluation, but dermoscopy can also be used.
Treatment:
Topical Permethrin massaged over the skin and removed some hours afterwards and repeated 7 days after. Efficacy is 90%, and in case of somebody in contact with an infected patient it can also be used as prophylaxis;
Oral ivermectin also seems to be effective, it is given as a single dose of 200 micrograms/Kg, repeated 7 days after. Efficacy is again >90%. It cannot be given to pregnant/lactating women or children under 15 Kg;
Older treatments: benzoyl-benzoate, topical sulfur, less used nowadays because of adverse skin reactions;

Figure 19

Crusted scabies is treated with topical permethrin at higher dose, applied every day for 7 days, then twice weekly until cured (much longer treatment) and it's suggested in combination with oral ivermectin on days 1, 2, 8, 9 and 15. It's much more difficult to treat and eradicate.

PRE-EXPOSURE PROPHYLAXIS (PREP)

In Italy it has been promoted and used mostly in STD clinics as part of a prevention package. Nowadays infection specialists can write down a prescription for PrEP, the patient buys it in the pharmacy. There's no reimbursement so they have to pay for the drugs entirely[18], oppositely to other countries (ex. France) in which if you are at risk of contracting HIV, you're under an STD clinic care and you receive the drugs for free.

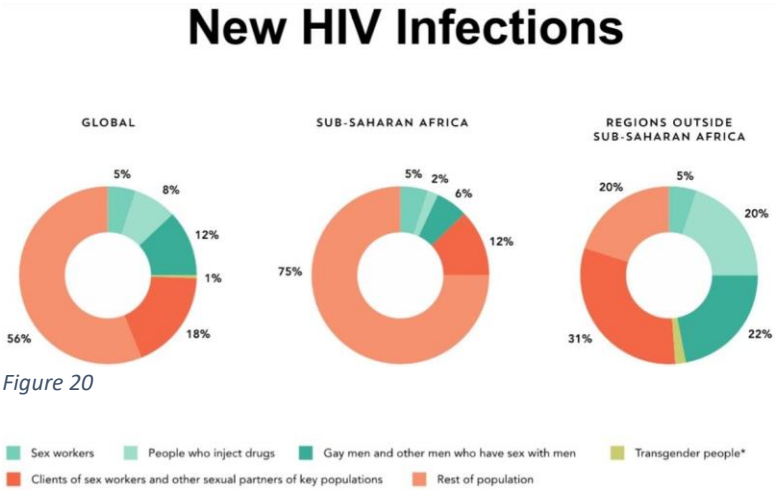


Figure 20

It has been demonstrated that it's cost-effective to prevent rather than treat these diseases once people at high risk get infected.
Remember two things:

- among new HIV infections outside sub-Saharan Africa, you have 20-25% of cases, or 30% in certain settings, discovered in MSM; therefore, MSM are one of the key groups in which you might have a high incidence of HIV infection;
- once you identify someone who has an STD, whatever it is, understand that he has a very high risk of contracting another STD, because of risky behaviors, because of no usage of condoms, because of the lesions that may increase the risk of getting *HIV*.

[18] nowadays they are generics, so the cost is lower, but still the drug is paid entirely by the patient

This study shows that patients diagnosed with syphilis had a super high risk of getting *HIV* in the two years after the first diagnosis. Those *HIV* diagnoses could have been prevented with counseling plus whatever intervention. So, they should include pre-exposure prophylaxis, because we know it's 90% effective in preventing *HIV*.

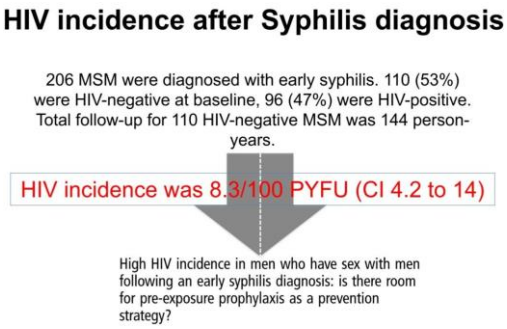


Figure 21

However, *HIV* prevention should be a combination of strategies, also because we know that just giving a magic pill is not a solution. Patients starting pre-exposure prophylaxis may have a slight increase in the risk of getting other STDs, probably because some people feel protected from *HIV*, so condom usage is slightly lower. In some studies, there was no effect, in some others a slight reduction in the use of condoms has been observed, so there was a higher incidence of other STDs.
HIV prevention is a combination of different things: subject that receives PrEP should also do counseling, scheduled visits for follow up, prevent other STDs etc.

Globally, taken outside the STD clinic, PrEP is a combination of:

- **Risk reduction**: condoms, syringe, methadone injection programs;
- **Early diagnosis**: in certain countries we have self-tests, oral tests for *HIV* that people can take and, if it's positive, there's a number to call to book an appointment and be followed by an *HIV* clinic;
- **Test and treat**: means that if I discover that someone has *HIV* I try to treat him as soon as possible, in order to reduce ongoing transmission;
- Unfortunately, the vaccine is still on its way;
- **PMTCT**: means prevention of mother to child transmission, because it's a very effective way to reduce numbers of new *HIV* positive patients;
- **PEP**: if there's a risk, post-exposure prophylaxis might work;
- **PREP**: it's just one piece of the puzzle;
- **Male circumcision:** it has been used in several low-resources countries in the last 20 years, with a reduction in the risk of getting *HIV* of 50-60%.

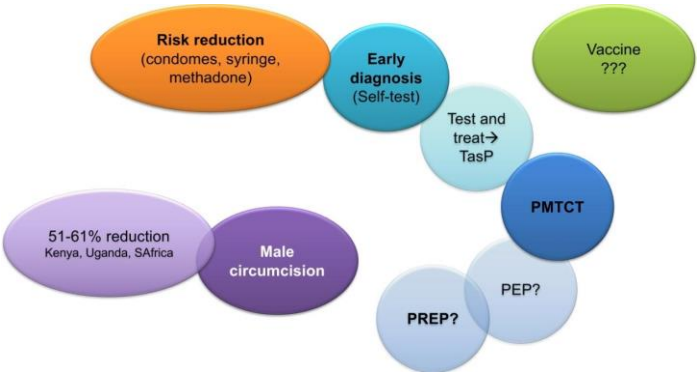


Figure 22

Again, combining all these interventions, we can reduce the incidence of *HIV* and probably get rid of it in a few years.
There are several approaches to pre-exposure prophylaxis, some are topical, which is very important because in certain settings women may not be able to discuss about safe sex, so it's something they can just provide for themselves without having to discuss it with partners. An example is **Tenofovir gel** that has been associated with reduction of *HIV* contraction. There's a vaginal ring **dapivirine** that has not been developed for treatment but only for prevention.
Most of the treatments are oral combinations of drugs: **Tenofovir** and **Emtricitabine** are two nucleoside analogues inhibitors of reverse transcriptase used for therapy. Some people were already taking them as prophylaxis before going to parties[19], and then randomized studies followed and demonstrated a very big

[19] he cites types of parties: dark room parties. I swear this guy :')

reduction in *HIV* risk. There are, still in phase 3, some drugs given intramuscular or subcutaneously every 2-3 months and they persist for a long time in blood and may prevent *HIV* transmission by inhibiting the virus in the vaginal, anal, oral mucosa (all mucosae that might be infected by *HIV*).

PrEP CLINICAL TRIALS

PrEP clinical trials

Study	population	size	location	drug	outcome
CAPRISA04	Hetero W	898	Africa	TDF gel	39%; 54% >80% of doses
iPrEX	MSM	2499	N-S Am,Oth	TDF/FTC	44%; 92%drug+
TDF2	Sex active	1200	Africa	TDF/FTC	63% protection
Pantners In PrEP	Hetero disc	4747	Africa	TDF/FTC or TDF	62% TDF alone; 73% TDF/FTC
PROUD	MSM	544	UK	TDF/FTC or 1 y deferral	86% reduction
IPERGAY	MSM	400	France	TDF/FTC on demand	86% reduction
FEM-PREP	Hetero W	1951	Africa	TDF/FTC	Trial discont. for futility
VOICE	Hetero W	5029	Africa	TDF or TDF/FTC or TFV gel	TDF discont. TFV gel disc TDF/FTC cont
HPTN052	H,MSM disc	1726;37	Africa, Oth	Immediate or delayed ART	96% protection

Figure 23

These are all the clinical trials suggesting reduction in the risk of *HIV* in different populations.
Those in red have been discontinued because of no effect and they were mostly performed on heterosexual women. The effectiveness of this strategy on women seems to be lower. There's probably one pharmacologically related reason: the concentrations that these drugs reach in the vagina are much lower compared to those reached in the anus, so the protection is much lower.
There's also need for high adherence to the clinical trial.
Professor: "you are not sick, it is a prevention and so adherence has been shown to be poor in certain settings".
Possible interpretation: heterosexual women are not affected by HIV and since this is just a prevention trial (and there might be less compliance to it), the response has been shown to be poor in certain settings, probably due to the fact that less people were adhering to the clinical trial compared to MSM.
The likely explanation for the reduced effect in PrEP CT in heterosexual women might be both the reduced effect of the drug and the reduced adherence to the CT.
On the other hand, in MSM the reduction in new infection was approximately 90%, hence very effective.
At the moment, there are two strategies that we can prescribe to patients if they fall in a higher risk profile (according to scores):

1. Patients take one pill once a day of tenofovir and emtricitabine called **Truvada;**
2. The second is an "on demand" or **event-driven pre-exposure prophylaxis** for patients that concentrate the number of partners in the weekends. Two pills should be taken 2-24 hours before sex[20], 1 pill 24 hours later and 1 pill 48 hours after first intake.

Both methods seem to be equally effective.

BARRIERS TO PrEP

Many colleagues consider this strategy wrong in terms of ethical considerations, but the professor says he doesn't understand because we're talking about risk reduction, not about what is better or worse. We are trying to reduce the risk of getting a chronic disease that is potentially deadly and costly to treat - it is also pragmatic. It's not the only intervention, it should be seen as part of a package intervention, **however ethical issues here are nonsense[21]**.
If you were to ask which are the most important barriers to pre-exposure prophylaxis in Europe, these are:

[20] NdR2: aridaje con 'sto dark room party: "to a dark room thing, to an event where they know something is going to happen"
[21] We love you Calcagno even if we can't see you

the cost is one of the most important, because patients must pay for drugs. Now the cost is 30-40 euros per month (drugs are generic);
the feasibility;
the risk of increasing other STIs;
the lower condom use.
Most important ones: cost and potential compensation risk for other STIs.

PrEP at Dean Street, London

Dean Street is an STD clinic in London in which patients can present at every hour, they have counseling, psychological services, they can do swabs for diagnosis and also deal with cum sex problems.
Cum sex is something growing in several cities in Europe and in the US and it increases the risk of contracting *HIV* at a very high level but also causes psychological problems, it's something that should be taken care of because of sexual health but also psychological health consequences.

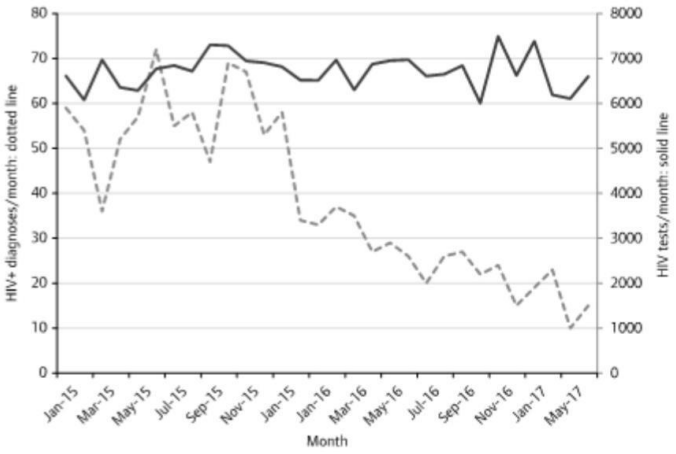


Figure 24

In Dean Street PrEP has been used for a long time, the black line in this graph (fig.13) is the number of tests per month: they test almost 6000 subjects per month, and the dotted line is the number of positive tests; there's no reduction in the number of *HIV* testing but there's a steep reduction in the number of *HIV* diagnosis. This is because PrEP and preventive counseling are used.

In fig.25 there is a comparison between three different clinics in the UK, where only one uses PrEP, while the other two don't. *HIV* incidence is going down only in the clinic that uses PrEP. To conclude, it's part of the task of STD clinics to counsel and prevent STIs but also *HIV*, and PrEP is one small piece of this puzzle.

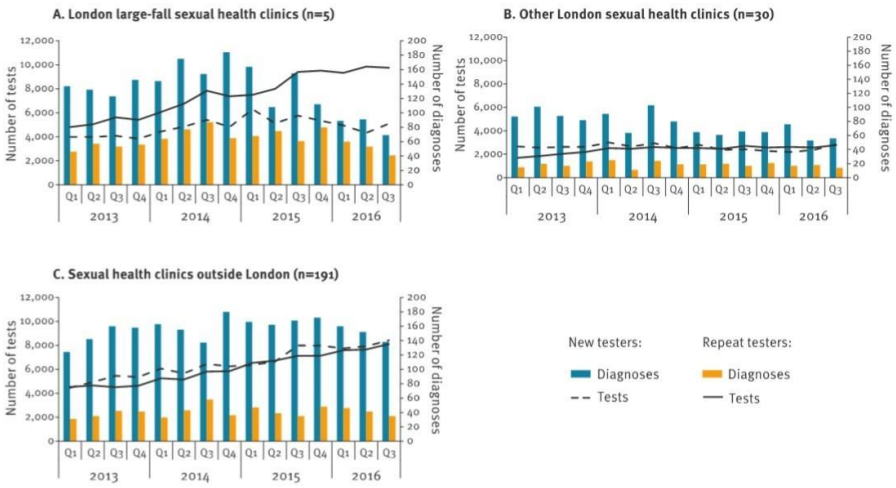


Figure 25

SEXUALLY TRANSMITTED INFECTIONS (STIS)/DISEASES (STDS)

GONORRHOEA- NEISSERIA GONORRHOEAE

Neisseria gonorrhea is a gram-negative diplococcus, very fragile in external environment. To grow in culture it needs specific means, it should be heated at 37° and kept in the heater, then examined and sent as soon as possible to the lab to preserve the culture.

- Incubation time is short, around few days (2-7);
- Signs and symptoms: it is associated with purulent urethritis, cervicitis and proctitis which are characterized by whitish and yellowish secretions with pruritus and pain (for this reason patients usually seek medical advice);
- Diagnosis is usually made with culture on urethral (PCR) and cervical swab;
- Treatment: straightforward, usually ceftriaxone at very low dose (250mg) or ciprofloxacin single dose - up to 1 gram. This can be done at alternative regimen although nowadays there are increasing rates of resistance to ATB[1] including fluoroquinolones, azithromycin, and ceftriaxone, all over the world but especially in the US and in Southeast Asia.
- It is important not only to trat the patient but to enforce the importance of notify the partner.

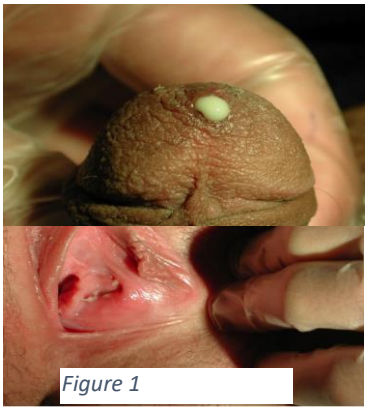


Figure 1

REITER'S SYNDROME

Also called **reactive arthritis**, mostly affecting large joints (especially lower limbs and knees) and it is asymmetrical. It might be associated with conjunctivitis and urethritis (sometimes gastroenteritis). It is associated with HLAB27+ genotype and it may present a few weeks after a gonococcal urethritis, but it is also associated with other bacteria, mainly gram-negative bacteria e.g. *Shigella* and *Yersinia* or *Chlamydia* as well.

CHLAMYDIA TRACHOMATIS

It is an obligate intracellular very small pathogen and there are different serovars divided in 3 classes:
A, B, C: causing trachoma, a conjunctivitis which can lead to blindness;
C to K: aspecific urethritis (e.g. cervicitis, salpingitis, proctitis), in women PID i.e. pelvic inflammatory disease, and potentially infertility;
L1 to L3: associated with Lymphogranuloma venereum, LGV.
Diagnosis: PCR for *Chlamydia* DNA in urines; also a swab can be used but it is much easier to do it in urine.
Treatment is azithromycin 1gr single dose (doxycycline can also be used). The combination of ceftriaxone and azithromycin will cure both *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.
Signs: **aspecific urethritis**, secretions, pruritus and pain when urinating.
Male will usually seek medical advice while females will not as it is mostly asymptomatic in females, which is why usually transmission is mediated by woman.
Complication: **Lymphogranuloma venereum** is associated with L1-L3 serovars of *Chlamydia trachomatis* with an incubation period of 5-21 days. It is more common in tropical countries. It has 3 phases:

Aspecific urethritis

Figure 2

LGV inguinal lymphadenitis

Figure 3

[1] antibodies

1. Chancroid, a non-painful ulcer, usually there is an inoculum of *Chlamydia* (remember: non-painful ulcers in genital area can be either LGV or syphilis);
2. After few days: painful satellite lymphadenitis with systemic symptoms (e.g. low-grade fever and malaise);
3. Chronic phase: acute proctitis/colitis with mucous purulent loss from anus, bloody stools, tenesmus, fever and pain. It is a hard DDX with IBDs due to similar signs and symptoms e.g. a lot of patients affected by LGV are wrongly diagnosed with RCU[2].

3. SYPHILIS - TREPONEMA PALLIDUM

It is not very easy to diagnose syphilis unless there are very clear signs and symptoms. The agent of syphilis is *Treponema pallidum* which is a motile gram-negative Spirochaeta.
The disease has 3 well-defined stages:

1. **Primary syphilis** (where the inoculum is) is characterized by non-painful ulcers in the genital, sometime oral, areas. Typically, the genital ones affect penis and vagina, while the oral ulcers can be harder to detect. Anal ulcers are usually almost impossible to detect since they are not painful;
2. **Secondary syphilis**: it usually occurs 4-10 weeks after primary syphilis and is characterized by fever, malaise, there is an interesting rough maculopapular rash, non-confluent and non-itchy. It is reddish-brown (rusty color) and involves the palms of the hands and the bottom of the feet[3]. This rash is very typical as it is one of the few rashes involving these parts of the body, so if you see them, think of syphilis and don't touch these rashes as they are very contagious (as they are full of *Treponema*)[4];

Figure 4

3. **Tertiary syphilis:** usually occurs if antibiotic treatment was not used in the previous phases, it occurs 10-15 years after the first infection. It is less common as antibiotics are more and more used in rich-resource countries. It occurs many years after infection and is characterized by granulomas (so called ***"syphilitic gummas"***) that can be detected in several organs (CNS, liver, aorta and several others). It may take between 10 to 30 years to develop from infection without any treatment due to the fact that antibiotic treatment somehow reduces the *Treponema* replication and the body reaction *to inflammation (ed)*, consisting in the development of granulomas in the body tissues.

Figure 5

STAGES AND TIME FRAMES OF SYPHILIS

[2] NdR2: RCU is the acronym in Italian for Rettocolite Ulcerosa, in English Ulcerative Colitis.
[3] "you should remember it!"
[4] Quote: "and I don't think it's a funny way to get syphilis"

Primary	Chancre, regional lymphadenopathy	3 wk (3–90 days)
Secondary	Rash, fever, malaise, lymphadenopathy, mucus lesions, condyloma lata, alopecia, meningitis, headaches	2–12 wk (2 wk–6 mos)
Latent	Asymptomatic	Early, <1 yr; late, >1 yr
Tertiary		
Cardiovascular syphilis	Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis	10–30 yr
Neurosyphilis		
Asymptomatic	None	
Acute syphilitic meningitis	Headache, meningeal irritation, confusion	<2 yr
Meningovascular	Cranial nerve palsies	
General paresis	Prodrome: headache, vertigo, personality disturbances, followed by acute vascular event with focal findings	5–7 yr
Tabes dorsalis	Insidious onset of dementia associated with delusional state, fatigue, intention tremors, loss of facial-muscle tone	10–20 yr
	Lightning pains, dysuria, ataxia, Argyll Robertson pupil, areflexia, loss of proprioception	15–20 yr
Gumma	Monocytic infiltrates with tissue destruction of any organ	1–46 yr (most cases 15 yr)

Figure 6

Complication: Neurosyphilis

It is thought to be the direct invasion of the CNS by *Treponema* but it is much more common in HIV+ patients and so when we find HIV+ patients with titer against *Treponema*, we treat them more aggressively by performing a lumbar puncture in order to rule out neurosyphilis.

It may have a very different clinical presentation: most of the patients will be asymptomatic, others can present with *aseptic meningitis*. Neurosyphilis is an important consequence that we should rule out when we see someone with aseptic meningitis.

However, the chronic forms are very common, including:

Meningovascular Syphilis (vascular problems of the brain);

General Paresis of Insane: it is a kind of paralytic dementia that mostly presents with psychiatric symptoms;

Tabe Dorsalis: characterized by nerve root pain, sensory ataxia and often ocular involvement.

These complications are very rare (the professor never saw Tabe Dorsalis in his life, he only saw two or three cases of General Paresis) but it is important to know them and think of these complications in case of some dementia especially if you work in a psychiatric ward or in a neurologic ward. Be aware of these possibilities and eventually test for syphilis.

Diagnosis:

To diagnose syphilis, the usual screening test is **Treponema immunoglobulin (IgG)**, if it is positive, the laboratory usually will directly run a **Non Treponemal test** (**VDRL**)[5] and a **Treponemal test (TPHA)**[6]. With the combination of these three tests we are able to estimate the stage of infection.

VDRL tells us the activity of the disease, and the VDRL titer should be followed over time to see if the therapy is effective or if maybe patients have been reinfected (especially in cases of immunosuppression).

After treatment, some patients will show a decrease in VDRL, then after reinfection they will show a new increase in VDRL and, every time, they will be exposed to new complications.

If we have a primary or secondary syphilis, we can perform a test of direct evidence by swabbing lesions and analyzing them in dark field microscopy (not so many labs have this) or PCR i.e. detection of *Treponema* DNA on these lesions is one of the way of demonstrating the presence of *Treponema*. Mostly in primary syphilis the serology is not that useful while direct PCR test is.

[5] Venereal Disease Research Laboratory test
[6] Treponema pallidum Haemagglutination Assay

Treatment:

Usually **Benzatil-Penicillin**[7] (2.4 millions of units) administered intramuscularly: 1 dose for primary syphilis and 3 doses for secondary syphilis (in this case doses are one week apart). This treatment is very painful (patient won't like you) and for this reason we also inject Lidocaine to reduce the muscle pain. Alternatively, we can use Ceftriaxone or Doxycycline.
Bear in mind that in secondary syphilis there could be the **Jarisch-Herxheimer reaction** which is an allergy to penicillin, it is the massive destruction of *Treponema*, so when we have a secondary syphilis, before the administration of penicillin, we should give a test dose of Amoxicillin and see if patient develops rash, hypotension or malaise, which are the typical signs of Herxheimer reaction. We usually give lots of steroid and follow the patient to see the progression.

4. CHANCROID - HAEMOPHILUS DUCREYI

Figure 7

It is really common in tropical areas, but you might also see it in Europe, even though it is uncommon.
"Chancroid" is the US way of describing "Ulcera molle", which are ulcers in genital areas (fig.10).
The agent is *Haemophilus ducreyi* whose incubation period is 3-5 days. Vesicles open in a chancroid (soft painful ulceration with basal exudate), which is more similar to herpes.
N.B. remember painful ulcers in genital areas!
We rely on clinical diagnosis as the sore is very hard to turn positive even with an appropriate lab technique. Treatment is ceftriaxone or ciprofloxacin or azithromycin; the same treatment of *Neisseria gonorrhoeae* will work for this STI.

5. HERPES GENITALIS

Figure 8

It is usually associated with *HSV2* (some cases *HSV1*) and patients present with highly painful ulcerations in genital areas, preceded by pain and paresthesias, sometimes also dysuria, leukorrhea and itch in genital areas.
Clinical presentation is very similar to *HSV1* (*Herpes labialis*), just in different regions. It is often recurrent (in more than 80% cases): it can come back every month and last for 7-10 days, the quality of life will be highly affected as you will have excruciating pain for 10/30 days and you cannot have sexual intercourse because it is painful and there's risk of contagion. For this reason, it will be a cause of distress for several patients which will lead them to search for medical treatment.
Diagnosis: typically clinical, based on history and clinical presentation. There is also serological diagnosis, which is specific for *HSV2* and it could help to rule it out by assessing the presence of antibodies against *HSV2* or run PCR by swabbing on this ulceration and looking for *HSV2* and *HSV1* DNA.
Treatment: Acyclovir or Valacyclovir (in pills), in case of frequent recurrences we may use suppressive treatment for a few months (usually 6) to reduce relapses and improve the patient quality of life of the patient.

[7] "so it is Depo Penicillin"

6. TRICHOMONIASIS - TRICHOMONAS VAGINALIS

Agent of Trichomoniasis is *Trichomonas vaginalis* which is a very mobile protozoon, it has a short-medium incubation period 4-28 days.
It usually causes very few symptoms:
in females: vaginitis with itch, dysuria, leukorrhea, dyspareunia. The discharged are characterized by a fishy odor, so usually the smell is bad, which is one of the reasons why many patients seek medical advice;
in males: usually asymptomatic urethritis.
Diagnosis is made on fresh smear obtained by swabbing the vaginal fluid and looking at fresh staining under the microscope. Under the microscope we can recognize the moving *Trichomonas* (fig.7).
Diagnosis can be also clinical due to the presence of liquid leukorrhea with typical fishy odor, but it has to be followed by smear examination. Also PCR can be done after collecting urine[8].


Figure 9

Treatment: Metronidazole 2 gr single dose (normally a combination of pills in a single dose) to the patient and his/her partner. During this period alcohol should be avoided as it will interfere with metronidazole giving GI reactions.
Incidence of *Trichomonas vaginalis* (*infection, ed*) is raising over time.
The *Trichomonas vaginalis* is visible under microscope: the fresh smear with the protozoa moving around can be seen.

7. GENITAL CANDIDIASIS

Candida is a commensal yeast which can be found in the skin, mouth, gut, vaginal flora. However, there are some predisposing conditions in which *Candida* will overgrow: diabetes, immune depression, microbiota alterations with reduced *lactobacilli* (antibiotics, mucositis, altered pH). It can be potentially transmittable, but it is very uncommon; in fact, when you analyze genetic strains in partners, 99% of the time the strains are different (only specific for the partner). Just a minority is found to be transmittable. We don't believe it is a contagious disease and for this reason we don't treat the partner in case of vaginal candidiasis.
Clinical presentation: itchy vulvovaginitis with whitish leukorrhea ("cottage cheese") due to the fact that it is more firm compared to *Trichomonas* (the aspect is cheesy). It can cause balanoposthitis with erythematous papules in men, but it is very uncommon as usually men don't have symptoms at all.
Diagnosis is mostly clinical. We might also perform an exudate culture, usually in patients that have recurrences, in order to rule out a resistance to fluconazole, which is one of the most used antifungal agents in this setting.

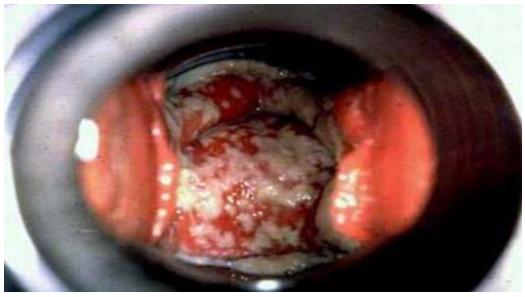


Figure 10

Treatment is usually local with ovules (clotrimazole, miconazole) or oral in severe cases (fluconazole, itraconazole). In case of frequent recurrences, suppressive therapy may be used to reduce the relapses which are usually associated with perimenstrual[9] period due to changes in pH and flora, for which *Candida* can

[8] Taken from slide 36 of 2019
[9] NdR2: He said "**premenopausal**"; however, I believe it should be **perimenstrual**. Indeed, hormonal fluctuations before the menstrual cycle can trigger changes in the bacteria in the vagina and high levels of estrogen cause *Candida* fungi to overgrow. Moreover, later he says "they have Candida in the days before menstruation".
NCBI: "daily colonization of Candida during the luteal phase of the menstrual cycle is described (...)

replicate faster and become the predominant species in vagina. Most of patients indeed will tell you that they have *Candida* in the days before menstruation.

8. CONDYLOMAS

HPV[10] causes Condylomata Acuminata, commonly known as genital warts.
Remember the difference with Condyloma Lata that are wart-like lesions caused by syphilis: secondary syphilis that instead of having a diffuse rash, presents with localized papules that look like condylomas but are syphilomas. Condylomas are most frequently associated with *HPV serotypes 6 and 11.* They can be external (genital areas, trunk) or internal condylomas.
Diagnosis is usually clinical.
Treatment[11] varies according to number of warts and their localization. It can be:
Removal (surgery, cryotherapy, cauterization);
Topical therapy (purified podophyllotoxin, imiquimod, sinecatechin) to reduce the dimension of the external warts and "make them fall off";
The vaccine specific for these serotypes could reduce the incidence of condylomas over time.

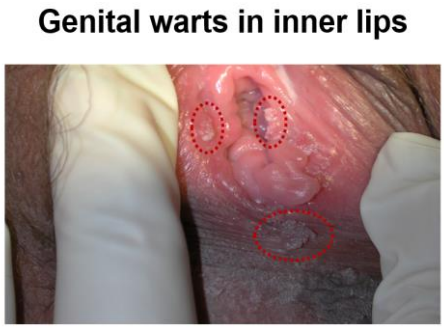


Figure 11

Figure 12

9. ECTOPARASITES

They are included in this lesson as they can be transmitted by sexual intercourse or by close contact with other people.

Some of these insects are:

- **Lice**: *Pediculus humanus* and *Phthirus pubis;*
- **Flies, Bedbugs and Fleas** are very common in certain areas. They normally don't directly cause diseases (even if potentially they can) but they can cause lesions that need to be differentiated from infectious lesions;
- **Mites** can cause diseases, especially *Sarcoptes scabiei* (the itch mite) which is the agent of scabies.

demonstrating an increase in the colony count preceding symptom development".
[10] will be discussed shortly since it will be a topic of both Oncology and Gynecology courses.
[11] it will probably be discussed also in the Dermatology course.

Insects		
1. Lice	*Pediculus humanus* (head or body louse)	Pruritus of scalp or trunk; nits (lendini) seen on hair shaft
	Phthirus pubis (pubic louse)	Pruritus in pubic area; nits seen on hair shaft
2. Flies	*Dermatobia hominis* (botfly)	Pruritic, painful, and erythematous nodule; larva may be seen emerging from nodule
3. Bedbugs	*Cimex lectularius* (common bedbug)	Pruritic, erythematous wheal (ponfo)
4. Fleas	*Pulex irritans* (house flea)	Pruritic, erythematous nodule
Arachnids		
1. Mites	*Sarcoptes scabiei* (itch mite)	Pruritic, erythematous papules, and linear tracks
2. Ticks	*Dermacentor species*	Ascending paralysis
3. Spiders	*Latrodectus mactans* (black widow spider)	Severe pain and muscle spasms
	Loxosceles reclusa (brown recluse spider)	Necrotic ulcer

Figure 13

9A. LICE

It is important for you to have an idea of the difference between head lice, body lice and pubic lice in terms of agents, symptoms. They can be visible as the adult insect or more commonly as nits (more visible than lice). Symptoms are similar and affect certain areas: they can cause discoloration of the skin, chronic itching, psychological problems but globally itch is the major symptom.

Figure 14

- Head lice: Pediculus humanus capitis (2-3 mm long)
- Body lice: Pediculus humanus humanus (2.3-3.6 mm long)
- Pubic lice (crabs): Phthirus pubis (1.1-1.8 mm long)[12]
Head lice found anywhere on the head (typically hair, but also can be found on the eyebrows).
Body lice: typically found on the clothing, except when they need a blood meal. They then move to the skin (but usually found on the clothing NOT the skin).
Pubic lice: usually found in pubic hair but are adapted to any other type of coarse hair (armpit region etc.)
All of the lice types are six-legged.
Differ on the basis of morphology (see pictures, especially pubic lice), where they can be found and size.

three types of lice[13]**:**

- They are ectoparasites, they live on the surface of the host, as opposed to inside the body (endoparasite) as with many other parasites we've seen. **Do** need blood meals to survive;
- Move by crawling, as opposed to flying or hopping, which affects the control and prevention measures needed;
- Feet are specifically adapted to human hair (cannot survive for that long if they fall off a human.) They can only live 1-2 days if they fall off of a human host;
- Have humans as their only host species, there is no animal reservoir, which makes control measures different and potentially simpler than other parasites;

[12] from slide 45
[13] Starting here until the end of paragraph "Epidemiology & risk factors" the information has been taken from the slides and notes professor made at the bottom.

- Have similar life cycles:
    - Egg/nit: usually located no more than 1/4 inches from the base of the human hair scalp. It's attached by a sticky glue-like substance secreted by the adult louse, which is what allows it to stick to the human hair. Takes 8-9 days to hatch;
    - Nymph (3 molts): There are three molting stages. Takes the nymphs approximately one week in total to move into the adult stage. The nymphs must take a blood meal in order to move on the next molting stage (therefore need three blood meals in total);
    - Adult: Can live up to 30 days on the human host. Die within 1-2 days without the human host. All adult lice need a blood meal in order to survive (nutrients). Females need it in particular for oviposition.

  Both nymphs and adults take blood meals from the human host.

Symptoms of HEAD and PUBIC lice:

- Itching: mostly due to the lice biting (people are somewhat allergic to the bite);
- Difficulty Sleeping: this is due to vector biology - the lice are more active at night, so biting and itching are more likely to occur at night;
- Sores and secondary bacterial infections from scratching: caused by scratching the itchy bites (and bacteria that's on the fingers or on the scalp can get into the bite). This is a minor symptom and isn't observed as often as the common itching!

Symptoms of BODY lice:

- Intense itching: more than head lice usually because there are more lice;
    - Skin discoloration/thickening: if infection is ongoing for a long period time (lots of lice bites), there can be skin discoloration and thickening in the areas with lots of bites.
    - Red rash appears where the lice have bitten;
    - Secondary bacterial infections from prolonged scratching: as with head lice, open wound → bacteria can enter from hands or surrounding skin area.

Diagnosis is based on direct visualization, i.e. observation of live nymphs or adult lice, made easier by using a fine-teeth comb and magnifying glass. Finding nits is suggestive of infection but not definitive.
Nits are very small, and it is difficult to correctly identify them. They are often mistaken for other things in the hair: dandruff, droplets of hairspray, etc.
Old nits can persist in the hair for a long time after infection (due to the sticky substance holding them to hair), so finding these old nits only indicates an old infection. Not necessarily an active infection that is still ongoing.
Lice are small, quick, and avoid the light (are most active at night).
In body lice, because lice are not normally found on the skin, you should look for them on the clothing. They can typically be found in the seams (along with nits)

EPIDEMIOLOGY & RISK FACTORS

- Head lice: “head-to-head transmission” since lice do not live very long without a human host and are not adapted to walking along smooth surfaces that do not have human hair. They are found worldwide, causes 6-12 million cases per year in the United States in children age 3-11. Typically occurs more often with children and in schools and is not associated with poor hygiene. Girls are at higher risk than boys, probably because of more social contact, playing with hair, etc. African American subjects are less affected than other groups because lice are specifically adapted to clinging the best to certain types of human hair;

- Pubic lice: worldwide prevalence estimated of 2%, it can spread through sexual contact and fomites (clothing, linens, towels belonging to an infected person. If found on children, pubic lice can be an indicator of sexual abuse;
- Body lice: associated with poor hygiene and crowded living conditions ex. prisons, homeless transient populations

Remember that body lice can transmit several bugs. Following a few "historical" examples:

- **Louse Borne Relapsing Fever** (caused by *Borrelia recurrentis*): there were several cases in migrants kept prisoners in Libya and through their journey to Italy. [14]*High case-fatality (10%) in WWII; mortality is 30-70% without treatment. It is more severe than the tick-borne version. Often found in epidemics amid poor-living conditions (and in war, like WWII) -- developing world. Spread when an uninfected human crushes an infected louse. B. recurrentis is spread via mucous membranes and then invades bloodstream. There is no animal reservoir and can alter the protein surface (causes relapses "relapsing fever"*);
- **Trench Fever** (caused by *Bartonella quintana*) during WWI. *It is rarely fatal with serious symptoms e.g. acute fever onset (five days), headache, myalgias, rashes, splenomegaly (less common)*;
- **Epidemic Typhus** (caused by *Rickettsia prowazekii*): *significant contributor to worldwide mortality (millions) before antibiotic treatment. It is classified as a category B bioterrorism agent (second most severe category) i.e. moderately easy to disseminate.*

If you find body lice, it is important to check also for these diseases, since some of these are being observed in certain areas of the world (limited resources-countries) in the setting of humanitarian problems and incarceration.

Lice Treatment[15]

- If only nits are visible (no nymphs or adult lice) probably the infection is not active and treatment may not be necessary, however it is suggested because lice nits are not easy to recognize. This treatment consist in **topical pediculicides** (there is resistance concern over the world): pyrethroids are the most used ones, in particular **permethrin at 1% concentration**, to be applied at day 0 and a second round 7-10 days, even 14, after;
- In case **body lice is present a higher (5%) concentration is preferred**, since the insect seems to be more resistant. A higher concentration is applied and left on for a few hours after application;
- **Oral ivermectin** is another option for lice in case topical treatments cannot be used. It was first used against onchocerciasis[16], but is also the drug of choice for strongyloidiasis[17] and is effective against scabies.

9B. SCABIES - SARCOPTES SCABIEI

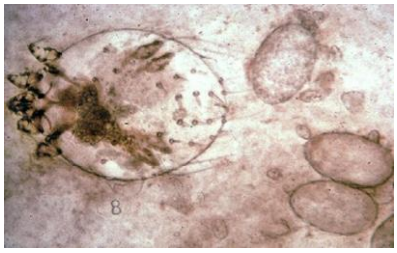


Figure 15

Prevalence of scabies is estimated to be high all over the world (at 100 million people), with however a high variability (0.2-71%), the highest rates are in limited resources settings and in Pacific and Latin American countries. It is also more common in crowded conditions, for example it can cause epidemics in long-term care facilities and prisons. Every time there is a case in the emergency room, panic breaks out. It's not really that highly contagious: you need to be in contact for some time with the skin of someone who has it to get

[14] Information in *italics* in this paragraph is taken from Professor's notes on powerpoint presentation

[15] "I think it is very common. Before losing my hair, when I was a child, I have been treated at least 5-6 times for hair lice" -cit

[16] From sbobinatore: Onchocerciasis, commonly known as "river blindness", is caused by the parasitic worm Onchocerca volvulus.

[17] From sbobinatore: Strongyloidiasis is a chronic parasitic infection of humans caused by Strongyloides stercoralis.

it. However, it can cause small epidemics and can be slightly contagious.
The pathogen is ***Sarcoptes scabiei***, an 8-legged mite. The females burrow into the epidermis after mating, and lay 2-3 eggs/day, but die after a few weeks. Larvae hatch in 3-4 days and as adults they can cause new rounds of infections and lesions. Usually there's a low parasitic burden, so 10-15 per host. However, in the crusted scabies, also called Norwegian scabies, that occurs in an immunosuppressed host, there can be millions of mites, and that's why it's more serious, harder to treat, and more contagious. The mites die if they're laid out of the body for a few hours: they need to be in contact with the host body for optimal temperature and nutrition.
Transmission is based on prolonged skin-to-skin contact, fomites are usually uncommon but important for crusted scabies and animals do not transmit the mites.

CLASSIC SCABIES

3-6 weeks after infestation, classic scabies begins. There's a severe pruritus everywhere on the body that worsens at night. There might also be an hypersensitivity reaction to mites, feces or eggs: patients might have not only the typical lesions caused by mites, but also an allergic reaction to mites' components throughout the body. The lesions are multiple, small, erythematous papules, often excoriated. You might see burrows, even if they are not easy to see. They are thin serpiginous lines of different colors and are diagnostically significant.
In these pictures you can see an inflammatory reaction (left) and a burrow (right)

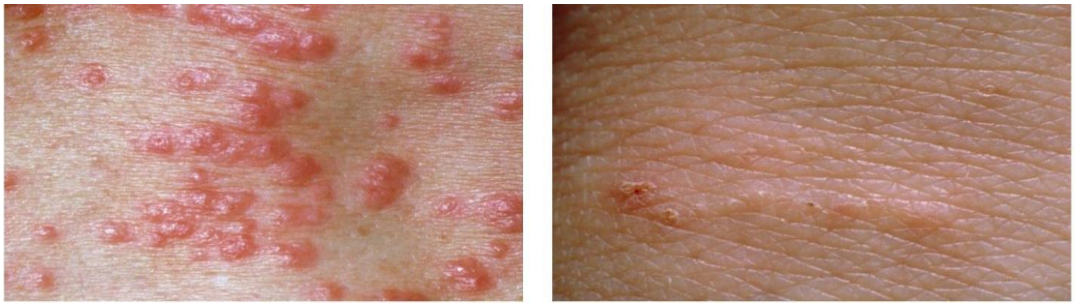


Figure 16

In fig.17, the most common places where you can find scabies lesions are in red, while the less common are in green, like the back and the head.

Remember to take a look between fingers and on the knees i.e. the two most common locations for scabies lesions.

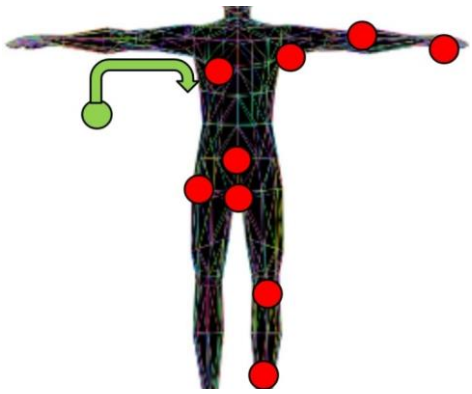


Figure 17

CRUSTED SCABIES (NORWEGIAN SCABIES)

It is the disease in immunosuppressed hosts, especially those with AIDS, lymphoma, or on chronic corticosteroids treatment. They have a very high mite burden, with less defined lesions resembling erythematous squamous patches that develop scales over them, as well as crusts, warts, fissures and they may smell badly because of underlying infection.
Complications: these lesions may complicate mostly with superinfections, usually from *staphylococci* or *streptococci*, that may cause impetigo, ecthyma, paronychia and furunculosis, potentially also

Figure 18

sepsis because of dissemination of gram-positive bacteria in all of the body through blood.
Diagnosis is usually clinical, according to presentation and risk factors. Skin scraping may help identifying mites at microscopical evaluation, but dermoscopy can also be used.
Treatment:
Topical Permethrin massaged over the skin and removed some hours afterwards and repeated 7 days after. Efficacy is 90%, and in case of somebody in contact with an infected patient it can also be used as prophylaxis;
Oral ivermectin also seems to be effective, it is given as a single dose of 200 micrograms/Kg, repeated 7 days after. Efficacy is again >90%. It cannot be given to pregnant/lactating women or children under 15 Kg;
Older treatments: benzoyl-benzoate, topical sulfur, less used nowadays because of adverse skin reactions;

Figure 19

Crusted scabies is treated with topical permethrin at higher dose, applied every day for 7 days, then twice weekly until cured (much longer treatment) and it's suggested in combination with oral ivermectin on days 1, 2, 8, 9 and 15. It's much more difficult to treat and eradicate.

PRE-EXPOSURE PROPHYLAXIS (PREP)

In Italy it has been promoted and used mostly in STD clinics as part of a prevention package. Nowadays infection specialists can write down a prescription for PrEP, the patient buys it in the pharmacy. There's no reimbursement so they have to pay for the drugs entirely[18], oppositely to other countries (ex. France) in which if you are at risk of contracting HIV, you're under an STD clinic care and you receive the drugs for free.

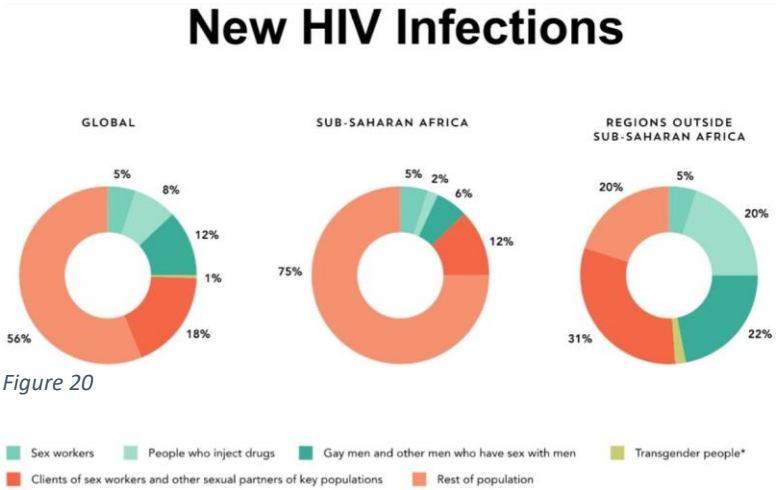


Figure 20

It has been demonstrated that it's cost-effective to prevent rather than treat these diseases once people at high risk get infected.
Remember two things:

- among new HIV infections outside sub-Saharan Africa, you have 20-25% of cases, or 30% in certain settings, discovered in MSM; therefore, MSM are one of the key groups in which you might have a high incidence of HIV infection;
- once you identify someone who has an STD, whatever it is, understand that he has a very high risk of contracting another STD, because of risky behaviors, because of no usage of condoms, because of the lesions that may increase the risk of getting *HIV*.

[18] nowadays they are generics, so the cost is lower, but still the drug is paid entirely by the patient

This study shows that patients diagnosed with syphilis had a super high risk of getting *HIV* in the two years after the first diagnosis. Those *HIV* diagnoses could have been prevented with counseling plus whatever intervention. So, they should include pre-exposure prophylaxis, because we know it's 90% effective in preventing *HIV*.

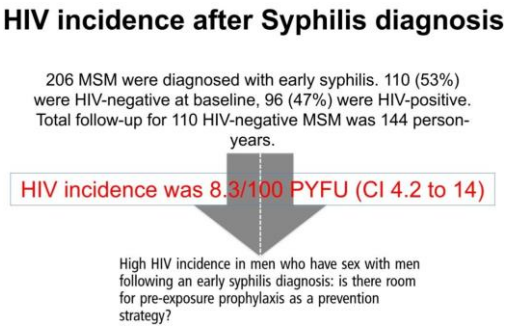


Figure 21

However, *HIV* prevention should be a combination of strategies, also because we know that just giving a magic pill is not a solution. Patients starting pre-exposure prophylaxis may have a slight increase in the risk of getting other STDs, probably because some people feel protected from *HIV*, so condom usage is slightly lower. In some studies, there was no effect, in some others a slight reduction in the use of condoms has been observed, so there was a higher incidence of other STDs.
HIV prevention is a combination of different things: subject that receives PrEP should also do counseling, scheduled visits for follow up, prevent other STDs etc.

Globally, taken outside the STD clinic, PrEP is a combination of:

- **Risk reduction**: condoms, syringe, methadone injection programs;
- **Early diagnosis**: in certain countries we have self-tests, oral tests for *HIV* that people can take and, if it's positive, there's a number to call to book an appointment and be followed by an *HIV* clinic;
- **Test and treat**: means that if I discover that someone has *HIV* I try to treat him as soon as possible, in order to reduce ongoing transmission;
- Unfortunately, the vaccine is still on its way;
- **PMTCT**: means prevention of mother to child transmission, because it's a very effective way to reduce numbers of new *HIV* positive patients;
- **PEP**: if there's a risk, post-exposure prophylaxis might work;
- **PREP**: it's just one piece of the puzzle;
- **Male circumcision:** it has been used in several low-resources countries in the last 20 years, with a reduction in the risk of getting *HIV* of 50-60%.

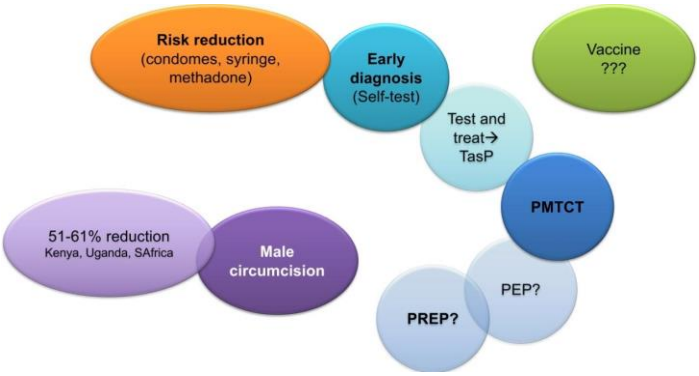


Figure 22

Again, combining all these interventions, we can reduce the incidence of *HIV* and probably get rid of it in a few years.
There are several approaches to pre-exposure prophylaxis, some are topical, which is very important because in certain settings women may not be able to discuss about safe sex, so it's something they can just provide for themselves without having to discuss it with partners. An example is **Tenofovir gel** that has been associated with reduction of *HIV* contraction. There's a vaginal ring **dapivirine** that has not been developed for treatment but only for prevention.
Most of the treatments are oral combinations of drugs: **Tenofovir** and **Emtricitabine** are two nucleoside analogues inhibitors of reverse transcriptase used for therapy. Some people were already taking them as prophylaxis before going to parties[19], and then randomized studies followed and demonstrated a very big

[19] he cites types of parties: dark room parties. I swear this guy :')

reduction in *HIV* risk. There are, still in phase 3, some drugs given intramuscular or subcutaneously every 2-3 months and they persist for a long time in blood and may prevent *HIV* transmission by inhibiting the virus in the vaginal, anal, oral mucosa (all mucosae that might be infected by *HIV*).

PrEP CLINICAL TRIALS

PrEP clinical trials

Study	population	size	location	drug	outcome
CAPRISA04	Hetero W	898	Africa	TDF gel	39%; 54% >80% of doses
iPrEX	MSM	2499	N-S Am,Oth	TDF/FTC	44%; 92%drug+
TDF2	Sex active	1200	Africa	TDF/FTC	63% protection
Pantners In PrEP	Hetero disc	4747	Africa	TDF/FTC or TDF	62% TDF alone; 73% TDF/FTC
PROUD	MSM	544	UK	TDF/FTC or 1 y deferral	86% reduction
IPERGAY	MSM	400	France	TDF/FTC on demand	86% reduction
FEM-PREP	Hetero W	1951	Africa	TDF/FTC	Trial discont. for futility
VOICE	Hetero W	5029	Africa	TDF or TDF/FTC or TFV gel	TDF discont. TFV gel disc TDF/FTC cont
HPTN052	H,MSM disc	1726;37	Africa, Oth	Immediate or delayed ART	96% protection

Figure 23

These are all the clinical trials suggesting reduction in the risk of *HIV* in different populations.
Those in red have been discontinued because of no effect and they were mostly performed on heterosexual women. The effectiveness of this strategy on women seems to be lower. There's probably one pharmacologically related reason: the concentrations that these drugs reach in the vagina are much lower compared to those reached in the anus, so the protection is much lower.
There's also need for high adherence to the clinical trial.
Professor: "you are not sick, it is a prevention and so adherence has been shown to be poor in certain settings".
Possible interpretation: heterosexual women are not affected by HIV and since this is just a prevention trial (and there might be less compliance to it), the response has been shown to be poor in certain settings, probably due to the fact that less people were adhering to the clinical trial compared to MSM.
The likely explanation for the reduced effect in PrEP CT in heterosexual women might be both the reduced effect of the drug and the reduced adherence to the CT.
On the other hand, in MSM the reduction in new infection was approximately 90%, hence very effective.
At the moment, there are two strategies that we can prescribe to patients if they fall in a higher risk profile (according to scores):

1. Patients take one pill once a day of tenofovir and emtricitabine called **Truvada;**
2. The second is an "on demand" or **event-driven pre-exposure prophylaxis** for patients that concentrate the number of partners in the weekends. Two pills should be taken 2-24 hours before sex[20], 1 pill 24 hours later and 1 pill 48 hours after first intake.

Both methods seem to be equally effective.

BARRIERS TO PrEP

Many colleagues consider this strategy wrong in terms of ethical considerations, but the professor says he doesn't understand because we're talking about risk reduction, not about what is better or worse. We are trying to reduce the risk of getting a chronic disease that is potentially deadly and costly to treat - it is also pragmatic. It's not the only intervention, it should be seen as part of a package intervention, **however ethical issues here are nonsense[21]**.
If you were to ask which are the most important barriers to pre-exposure prophylaxis in Europe, these are:

[20] NdR2: aridaje con 'sto dark room party: "to a dark room thing, to an event where they know something is going to happen"
[21] We love you Calcagno even if we can't see you

the cost is one of the most important, because patients must pay for drugs. Now the cost is 30-40 euros per month (drugs are generic);
the feasibility;
the risk of increasing other STIs;
the lower condom use.
Most important ones: cost and potential compensation risk for other STIs.

PrEP at Dean Street, London

Dean Street is an STD clinic in London in which patients can present at every hour, they have counseling, psychological services, they can do swabs for diagnosis and also deal with cum sex problems.
Cum sex is something growing in several cities in Europe and in the US and it increases the risk of contracting *HIV* at a very high level but also causes psychological problems, it's something that should be taken care of because of sexual health but also psychological health consequences.

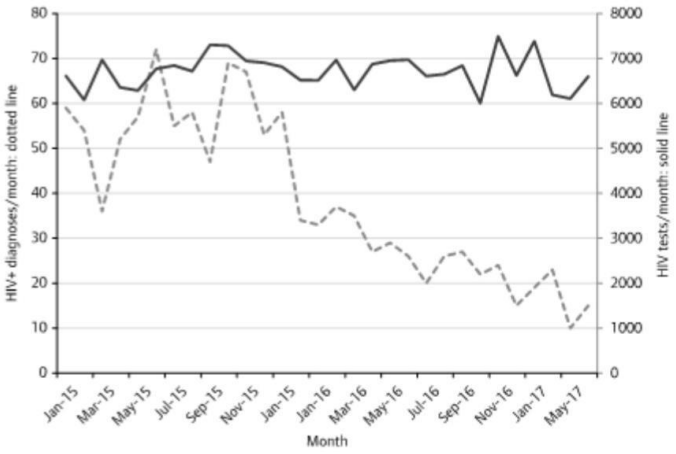


Figure 24

In Dean Street PrEP has been used for a long time, the black line in this graph (fig.13) is the number of tests per month: they test almost 6000 subjects per month, and the dotted line is the number of positive tests; there's no reduction in the number of *HIV* testing but there's a steep reduction in the number of *HIV* diagnosis. This is because PrEP and preventive counseling are used.

In fig.25 there is a comparison between three different clinics in the UK, where only one uses PrEP, while the other two don't. *HIV* incidence is going down only in the clinic that uses PrEP. To conclude, it's part of the task of STD clinics to counsel and prevent STIs but also *HIV*, and PrEP is one small piece of this puzzle.

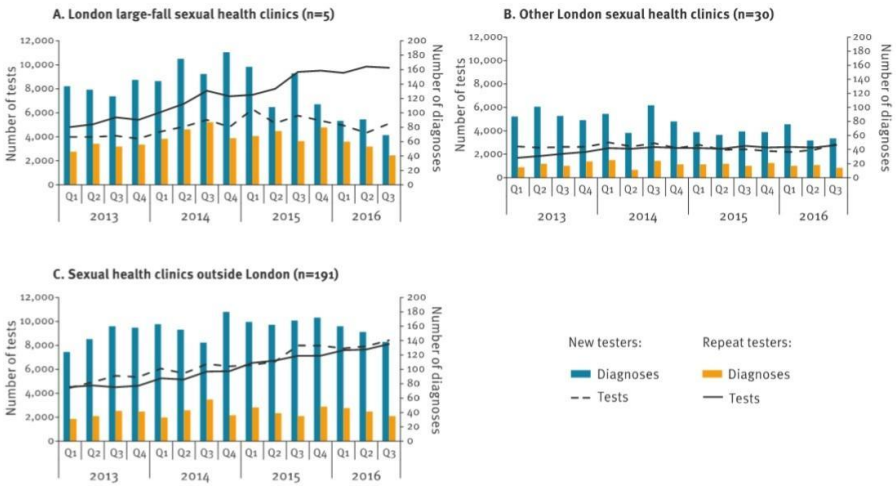


Figure 25