

**WAKE UP!**

**A GUIDE TO  
SEXUALLY  
TRANSMITTED  
DISEASES &  
VIRUSES**

EDITED BY

**JONAH SANDERS**



# Wake Up



Jonah Sanders

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## Bacterial Vaginosis

Bacterial vaginosis (BV) is a disease of the vagina caused by excessive growth of bacteria.

Common symptoms include increased vaginal discharge that often smells like fish. The discharge is usually white or gray in color. Burning with urination may occur. Itching is uncommon. Occasionally, there may be no symptoms. Having BV approximately doubles the risk of infection by a number of sexually transmitted infections, including HIV/AIDS. It also increases the risk of early delivery among pregnant women.

BV is caused by an imbalance of the naturally occurring bacteria in the vagina. There is a change in the most common type of bacteria and a hundred to thousandfold increase in total numbers of bacteria present. Typically, bacteria other than Lactobacilli become more common. Risk factors include douching, new or multiple sex partners, antibiotics, and using an intrauterine device, among others. However, it is not considered a sexually transmitted infection. Diagnosis is suspected based on the symptoms, and may be verified by testing the vaginal discharge and finding a higher than normal vaginal pH, and large numbers of bacteria. BV is often confused with a vaginal yeast infection or infection with *Trichomonas*.

Usually treatment is with an antibiotic, such as clindamycin or metronidazole. These medications may also be used in the second or third trimesters of pregnancy. However, the condition often recurs following treatment. Probiotics may help prevent re-occurrence. It is unclear if the use of probiotics or antibiotics affects pregnancy outcomes.

BV is the most common vaginal infection in women of reproductive age. The percentage of women affected at any given time varies between 5% and 70%. BV is most common in parts of Africa and least common in Asia and Europe. In the United States about 30% of women between the ages of 14 and 49 are affected. Rates vary considerably between ethnic groups within a country. While BV-like symptoms have been described for much of recorded history, the first clearly documented case occurred in 1894.

Healthy vaginal microbiota consists of species which neither cause symptoms or infections, nor negatively affect pregnancy. It is dominated mainly by Lactobacillus species. BV is defined by the disequilibrium in the vaginal microbiota, with decline in the number of lactobacilli. While the infection involves a number of bacteria, it is believed that most infections start with *Gardnerella vaginalis* creating a biofilm, which allows other opportunistic bacteria to thrive.

One of the main risks for developing BV is douching, which alters the vaginal microbiota and predisposes women to developing BV. Douching is strongly discouraged by the U.S. Department of Health and Human Services and various medical authorities, for this and other reasons. BV is a risk factor for pelvic inflammatory disease, HIV, sexually transmitted infections (STIs), and reproductive and obstetric disorders or negative outcomes. It is possible for sexually inactive persons to develop bacterial vaginosis.

Bacterial vaginosis may sometimes affect women after menopause. Also, subclinical iron deficiency may correlate with bacterial vaginosis in early pregnancy. A longitudinal study published in February 2006, in the American Journal of Obstetrics and Gynecology, showed a link between psychosocial stress and bacterial vaginosis persisted even when other risk factors were taken into account. Exposure to the spermicide nonoxynol-9 does not affect the risk of developing bacterial vaginosis.

Having a female partner increases the risk of BV by 60%. The bacteria associated with BV have been isolated from male genitalia. BV microbiota has been found in the penis, coronal sulcus, and male urethra, in the male partners of infected females. Partners who have not been circumcised may act as a 'reservoir' increasing the likelihood of acquiring an infection after sexual intercourse. Another mode of transmission of the BV-associated microbiota is to a female sexual partner via skin-to-skin transfer. BV may be transmitted via the perineal enteric bacteria from the microbiota of the female and male genitalia.

To make a diagnosis of bacterial vaginosis, a swab from inside the vagina should be obtained.

These swabs can be tested for:



Gram stain which shows the depletion of lactobacilli and overgrowth of *Gardnerella vaginalis* bacteria. Bacterial vaginosis is usually confirmed by a Gram stain of vaginal secretions.

A characteristic "fishy" odor on wet mount. This test, called the whiff test, is performed by adding a small amount of potassium hydroxide to a microscopic slide containing the vaginal discharge. A characteristic fishy odor is considered a positive whiff test and is suggestive of bacterial vaginosis.

Loss of acidity. To control bacterial growth, the vagina is normally slightly acidic with a pH of 3.8–4.2. A swab of the discharge is put onto litmus paper to check its acidity. A pH greater than 4.5 is considered alkaline and is suggestive of bacterial vaginosis.

The presence of clue cells on wet mount. Similar to the whiff test, the test for clue cells is performed by placing a drop of sodium chloride solution on a slide containing vaginal discharge. If present, clue cells can be visualized under a microscope. They are so-named because they give a clue to the reason behind the discharge. These are epithelial cells that are coated with bacteria.

Differential diagnosis for bacterial vaginosis includes the following: Normal vaginal discharge.

Candidiasis (thrush, or a yeast infection).

Trichomoniasis, an infection caused by *Trichomonas vaginalis*.

Aerobic vaginitis.

The Center for Disease Control (CDC) defines STIs as "a variety of clinical syndromes and infections caused by pathogens that can be acquired and transmitted through sexual activity." But the CDC does not specifically identify BV as sexually transmitted infection.

Amsel criteria In clinical practice BV can be diagnosed using the Amsel criteria: Thin, white, yellow, homogeneous discharge.

Clue cells on microscopy.

pH of vaginal fluid  $>4.5$  Release of a fishy odor on adding alkali—10% potassium hydroxide (KOH) solution.

At least three of the four criteria should be present for a confirmed diagnosis. A modification of the Amsel criteria accepts the presence of two instead of three factors and is considered equally diagnostic.

Gram stain An alternative is to use a Gram-stained vaginal smear, with the Hay/Ison criteria or the Nugent criteria. The Hay/Ison criteria are defined as follows:

Grade 1 (Normal): Lactobacillus morphotypes predominate.

Grade 2 (Intermediate): Some lactobacilli present, but *Gardnerella* or *Mobiluncus* morphotypes also present.

Grade 3 (Bacterial Vaginosis): Predominantly *Gardnerella* and/or *Mobiluncus* morphotypes. Few or absent lactobacilli. (Hay et al., 1994) *Gardnerella vaginalis* is the main culprit in BV. *Gardnerella vaginalis* is a short rod (coccobacillus). Hence, the presence of clue cells and gram variable coccobacilli are indicative or diagnostic of bacterial vaginosis.

Nugent score The Nugent score is now rarely used by physicians due to the time it takes to read the slides and requires the use of a trained microscopist. A score of 0–10 is generated from combining three other scores. The scores are as follows:

0–3 is considered negative for BV 4–6 is considered intermediate 7+ is considered indicative of BV.



At least 10–20 high power (1000× oil immersion) fields are counted and an average determined.

Some steps suggested to lower the risk include: not douching, avoiding sex, or limiting the number of sex partners.

One review concluded that probiotics may help prevent re-occurrence. Another review found that, while there is tentative evidence, it is not strong enough to recommend their use for this purpose.

Early evidence suggested that antibiotic treatment of male partners could re-establish the normal microbiota of the male urogenital tract and prevent the recurrence of infection. However, a 2016 Cochrane review found high-quality evidence that treating the sexual partners of women with bacterial vaginosis had no effect on symptoms, clinical outcomes, or recurrence in the affected women. It also found that such treatment may lead treated sexual partners to report increased adverse events.

Treatment is typically with the antibiotics metronidazole or clindamycin. They can be either given by mouth or applied inside the vagina with similar efficacy. About 10% to 15% of people, however, do not improve with the first course of antibiotics and recurrence rates of up to 80% have been documented. Recurrence rates are increased with sexual activity with the same pre/posttreatment partner and inconsistent condom use although estrogen-containing contraceptives decrease recurrence. When clindamycin is given to pregnant women symptomatic with BV before 22 weeks of gestation the risk of pre-term birth before 37 weeks of gestation is lower.

Other antibiotics that may work include macrolides, lincosamides, nitroimidazoles, and penicillins.

Bacterial vaginosis is not considered a sexually transmitted infection, and treatment of a male sexual partner of a woman with bacterial vaginosis is not recommended.

#### Probiotics

A 2009 Cochrane review found tentative but insufficient evidence for probiotics as a treatment for BV. A 2014 review reached the same conclusion. A 2013 review found some evidence supporting the use of probiotics during pregnancy. The preferred probiotics for BV are those containing high doses of lactobacilli (around 10<sup>9</sup> CFUs) given in the vagina.

Intravaginal administration is preferred to taking them by mouth. Prolonged repetitive courses of treatment appear to be more promising than short courses.

#### Antiseptics

Topical antiseptics, for example dequalinium chloride, policresulen, hexetidine or povidone iodine vaginal suppositories may be applied, if the risk of ascending infections is low (outside of pregnancy and in immunocompetent people without histories of upper genital tract infections).

One study found that vaginal irrigations with hydrogen peroxide (3%) resulted in a slight improvement but this was much less than with the use of oral metronidazole.



## Chlamydia

Chlamydia, or more specifically a chlamydia infection, is a sexually transmitted infection caused by the bacterium *Chlamydia trachomatis*. Most people who are infected have no symptoms. When symptoms do appear they may occur only several weeks after infection; the incubation period between exposure and being able to infect others is thought to be on the order of two to six weeks. Symptoms in women may include vaginal discharge or burning with urination.

Symptoms in men may include discharge from the penis, burning with urination, or pain and swelling of one or both testicles. The infection can spread to the upper genital tract in women, causing pelvic inflammatory disease, which may result in future infertility or ectopic pregnancy.

Chlamydia infections can occur in other areas besides the genitals, including the anus, eyes, throat, and lymph nodes. Repeated chlamydia infections of the eyes that go without treatment can result in trachoma, a common cause of blindness in the developing world.

Chlamydia can be spread during vaginal, anal, or oral sex, and can be passed from an infected mother to her baby during childbirth. The eye infections may also be spread by personal contact, flies, and contaminated towels in areas with poor sanitation. Infection by the bacterium *Chlamydia trachomatis* only occurs in humans. Diagnosis is often by screening which is recommended yearly in sexually active women under the age of twenty-five, others at higher risk, and at the first prenatal visit. Testing can be done on the urine or a swab of the cervix, vagina, or urethra.

Rectal or mouth swabs are required to diagnose infections in those areas.

Prevention is by not having sex, the use of condoms, or having sex with only one other person, who is not infected. Chlamydia can be cured by antibiotics with typically either azithromycin or doxycycline being used. Erythromycin or azithromycin is recommended in babies and during pregnancy. Sexual partners should also be treated, and infected people should be advised not to have sex for seven days and until symptom free. Gonorrhea, syphilis, and HIV should be tested for in those who have been infected. Following treatment people should be tested again after three months.

Chlamydia is one of the most common sexually transmitted infections, affecting about 4.2% of women and 2.7% of men worldwide. In 2015, about 61 million new cases occurred globally.

In the United States about 1.4 million cases were reported in 2014. Infections are most common among those between the ages of 15 and 25 and are more common in women than men. In 2015 infections resulted in about 200 deaths. The word chlamydia is from the Greek *χλαμύδα*, meaning "cloak".

### Signs and symptoms

#### Genital disease

Inflammation of the cervix from chlamydia infection characterized by mucopurulent cervical discharge, redness, and inflammation. A white, cloudy or watery discharge may emerge from the tip of the penis.

#### Women

Chlamydial infection of the cervix (neck of the womb) is a sexually transmitted infection which has no symptoms for around 70% of women infected. The infection can be passed through vaginal, anal, or oral sex. Of those who have an asymptomatic infection that is not detected by their doctor, approximately half will develop pelvic inflammatory disease (PID), a generic term for infection of the uterus, fallopian tubes, and/or ovaries. PID can cause scarring inside the reproductive organs, which can later cause serious complications, including chronic pelvic pain, difficulty becoming pregnant, ectopic (tubal) pregnancy, and other dangerous complications of pregnancy. Chlamydia is known as the "silent epidemic", as at least 70% of genital *C. trachomatis* infections in women (and 50% in men) are asymptomatic at the time of diagnosis, and can linger for months or years before being discovered. Signs and symptoms may include abnormal vaginal bleeding or



discharge, abdominal pain, painful sexual intercourse, fever, painful urination or the urge to urinate more often than usual (urinary urgency). For sexually active women who are not pregnant, screening is recommended in those under 25 and others at risk of infection.

Risk factors include a history of chlamydial or other sexually transmitted infection, new or multiple sexual partners, and inconsistent condom use. Guidelines recommend all women attending for emergency contraceptive are offered chlamydia testing, with studies showing up to 9% of women aged <25 years had chlamydia.

#### Men

In men, those with a chlamydial infection show symptoms of infectious inflammation of the urethra in about 50% of cases. Symptoms that may occur include: a painful or burning sensation when urinating, an unusual discharge from the penis, testicular pain or swelling, or fever. If left untreated, chlamydia in men can spread to the testicles causing epididymitis, which in rare cases can lead to sterility if not treated. Chlamydia is also a potential cause of prostatic inflammation in men, although the exact relevance in prostatitis is difficult to ascertain due to possible contamination from urethritis.

#### Eye disease

Trachoma is a chronic conjunctivitis caused by *Chlamydia trachomatis*. It was once the leading cause of blindness worldwide, but its role diminished from 15% of blindness cases by trachoma in 1995 to 3.6% in 2002. The infection can be spread from eye to eye by fingers, shared towels or cloths, coughing and sneezing and eye-seeking flies. Symptoms include mucopurulent ocular discharge, irritation, redness, and lid swelling. Newborns can also develop chlamydia eye infection through childbirth. Using the SAFE strategy (acronym for surgery for in-growing or inturned lashes, antibiotics, facial cleanliness, and environmental improvements), the World Health Organization aims for the global elimination of trachoma by 2020 (GET 2020 initiative).

#### Joints

Chlamydia may also cause reactive arthritis—the triad of arthritis, conjunctivitis and urethral inflammation—especially in young men. About 15,000 men develop reactive arthritis due to chlamydia infection each year in the U.S., and about 5,000 are permanently affected by it. It can occur in both sexes, though is more common in men.

#### Infants

As many as half of all infants born to mothers with chlamydia will be born with the disease.

Chlamydia can affect infants by causing spontaneous abortion; premature birth; conjunctivitis, which may lead to blindness; and pneumonia. Conjunctivitis due to chlamydia typically occurs one week after birth (compared with chemical causes (within hours) or gonorrhoea (2–5 days)).

#### Other conditions

A different serovar of *Chlamydia trachomatis* is also the cause of lymphogranuloma venereum, an infection of the lymph nodes and lymphatics. It usually presents with genital ulceration and swollen lymph nodes in the groin, but it may also manifest as rectal inflammation, fever or swollen lymph nodes in other regions of the body.

Chlamydiae have the ability to establish long-term associations with host cells. When an infected host cell is starved for various nutrients such as amino acids (for example, tryptophan), iron, or vitamins, this has a negative consequence for Chlamydiae since the organism is dependent on the host cell for these nutrients. Long-term cohort studies indicate that approximately 50% of those infected clear within a year, 80% within two years, and 90% within three years.

The starved chlamydiae enter a persistent growth state wherein they stop cell division and become morphologically aberrant by increasing in size. Persistent organisms remain viable as they are capable of returning to a normal growth state once conditions in the host cell improve.



There is debate as to whether persistence has relevance. Some believe that persistent chlamydiae are the cause of chronic chlamydial diseases. Some antibiotics such as  $\beta$ -lactams have been found to induce a persistent-like growth state.

The diagnosis of genital chlamydial infections evolved rapidly from the 1990s through 2006.

Nucleic acid amplification tests (NAAT), such as polymerase chain reaction (PCR), transcription mediated amplification (TMA), and the DNA strand displacement amplification (SDA) now are the mainstays. NAAT for chlamydia may be performed on swab specimens sampled from the cervix (women) or urethra (men), on self-collected vaginal swabs, or on voided urine. NAAT has been estimated to have a sensitivity of approximately 90% and a specificity of approximately 99%, regardless of sampling from a cervical swab or by urine specimen. In women seeking an sexually transmitted infection (STI) clinic and a urine test is negative, a subsequent cervical swab has been estimated to be positive in approximately 2% of the time.

At present, the NAATs have regulatory approval only for testing urogenital specimens, although rapidly evolving research indicates that they may give reliable results on rectal specimens.

Because of improved test accuracy, ease of specimen management, convenience in specimen management, and ease of screening sexually active men and women, the NAATs have largely replaced culture, the historic gold standard for chlamydia diagnosis, and the non-amplified probe tests. The latter test is relatively insensitive, successfully detecting only 60–80% of infections in asymptomatic women, and often giving falsely-positive results. Culture remains useful in selected circumstances and is currently the only assay approved for testing non-genital specimens.

Other methods also exist including: ligase chain reaction (LCR), direct fluorescent antibody testing, enzyme immunoassay, and cell culture.

Rapid point-of-care tests are, as of 2020, not thought to be effective for diagnosing chlamydia in men of reproductive age and nonpregnant women because of high false-negative rates.

*C. trachomatis* infection can be effectively cured with antibiotics. Guidelines recommend azithromycin, doxycycline, erythromycin, levofloxacin or ofloxacin. In men, doxycycline (100 mg twice a day for 7 days) is probably more effective than azithromycin (1 g single dose) but evidence for the relative effectiveness of antibiotics in women is very uncertain. Agents recommended during pregnancy include erythromycin or amoxicillin.

An option for treating sexual partners of those with chlamydia or gonorrhea includes patient-delivered partner therapy (PDT or PDPT), which is the practice of treating the sex partners of index cases by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner.

Following treatment people should be tested again after three months to check for reinfection.



## Gonorrhea

Gonorrhea, colloquially known as the clap, is a sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae*. Infection may involve the genitals, mouth, or rectum. Infected men may experience pain or burning with urination, discharge from the penis, or testicular pain. Infected women may experience burning with urination, vaginal discharge, vaginal bleeding between periods, or pelvic pain. Complications in women include pelvic inflammatory disease and in men include inflammation of the epididymis. Many of those infected, however, have no symptoms. If untreated, gonorrhea can spread to joints or heart valves.

Gonorrhea is spread through sexual contact with an infected person. This includes oral, anal, and vaginal sex. It can also spread from a mother to a child during birth. Diagnosis is by testing the urine, urethra in males, or cervix in females. Testing all women who are sexually active and less than 25 years of age each year as well as those with new sexual partners is recommended; the same recommendation applies in men who have sex with men (MSM).

Gonorrhea can be prevented with the use of condoms, having sex with only one person who is uninfected, and by not having sex. Treatment is usually with ceftriaxone by injection and azithromycin by mouth. Resistance has developed to many previously used antibiotics and higher doses of ceftriaxone are occasionally required. Retesting is recommended three months after treatment.

Sexual partners from the last two months should also be treated.

Gonorrhea affects about 0.8% of women and 0.6% of men. An estimated 33 to 106 million new cases occur each year, out of the 498 million new cases of curable STI – which also includes syphilis, chlamydia, and trichomoniasis. Infections in women most commonly occur when they are young adults. In 2015, it caused about 700 deaths. Descriptions of the disease date back to before the Common Era within the Old Testament. The current name was first used by the Greek physician Galen before 200 AD who referred to it as "an unwanted discharge of semen".

Gonorrhea infections of mucosal membranes can cause swelling, itching, pain, and the formation of pus. The time from exposure to symptoms is usually between two and 14 days, with most symptoms appearing between four and six days after infection, if they appear at all. Both men and women with infections of the throat may experience a sore throat, though such infection does not produce symptoms in 90% of cases. Other symptoms may include swollen lymph nodes around the neck. Either sex can become infected in the eyes or rectum if these tissues are exposed to the bacterium.

**Women** Half of women with gonorrhea are asymptomatic but the other half experience vaginal discharge, lower abdominal pain, or pain with sexual intercourse associated with inflammation of the uterine cervix. Common medical complications of untreated gonorrhea in women include pelvic inflammatory disease which can cause scars to the fallopian tubes and result in later ectopic pregnancy among those women who become pregnant.

### Men

Most infected men with symptoms have inflammation of the penile urethra associated with a burning sensation during urination and discharge from the penis. In men, discharge with or without burning occurs in half of all cases and is the most common symptom of the infection. This pain is caused by a narrowing and stiffening of the urethral lumen. The most common medical complication of gonorrhea in men is inflammation of the epididymis.

Gonorrhea is also associated with increased risk of prostate cancer. Infants

If not treated, gonococcal ophthalmia neonatorum will develop in 28% of infants born to women with gonorrhea.

### Spread

If left untreated, gonorrhea can spread from the original site of infection and infect and damage the joints, skin, and other organs. Indications of this can include fever, skin rashes, sores, and joint pain and swelling. In advanced cases, gonorrhea may cause a general feeling of tiredness similar to other infections. It is also possible



for an individual to have an allergic reaction to the bacteria, in which case any appearing symptoms will be greatly intensified. Very rarely it may settle in the heart, causing endocarditis, or in the spinal column, causing meningitis. Both are more likely among individuals with suppressed immune systems, however.

Traditionally, gonorrhoea was diagnosed with Gram stain and culture; however, newer polymerase chain reaction (PCR)-based testing methods are becoming more common. In those failing initial treatment, culture should be done to determine sensitivity to antibiotics.

Tests that use PCR (aka nucleic acid amplification) to identify genes unique to *N. gonorrhoeae* are recommended for screening and diagnosis of gonorrhoea infection. These PCR-based tests require a sample of urine, urethral swabs, or cervical/vaginal swabs. Culture (growing colonies of bacteria in order to isolate and identify them) and Gram-stain (staining of bacterial cell walls to reveal morphology) can also be used to detect the presence of *N. gonorrhoeae* in all specimen types except urine.

If Gram-negative, oxidase-positive diplococci are visualized on direct Gram stain of urethral pus (male genital infection), no further testing is needed to establish the diagnosis of gonorrhoea infection. However, in the case of female infection direct Gram stain of cervical swabs is not useful because the *N. gonorrhoeae* organisms are less concentrated in these samples. The chances of false positives are increased as Gram-negative diplococci native to the normal vaginal flora cannot be distinguished from *N. gonorrhoeae*. Thus, cervical swabs must be cultured under the conditions described above. If oxidase positive, Gram-negative diplococci are isolated from a culture of a cervical/vaginal swab specimen, then the diagnosis is made. Culture is especially useful for diagnosis of infections of the throat, rectum, eyes, blood, or joints—areas where PCR-based tests are not well established in all labs. Culture is also useful for antimicrobial sensitivity testing, treatment failure, and epidemiological purposes (outbreaks, surveillance).

In patients who may have disseminated gonococcal infection (DGI), all possible mucosal sites should be cultured (e.g., pharynx, cervix, urethra, rectum). Three sets of blood cultures should also be obtained. Synovial fluid should be collected in cases of septic arthritis.

All people testing positive for gonorrhoea should be tested for other sexually transmitted diseases such as chlamydia, syphilis, and human immunodeficiency virus. Studies have found co-infection with chlamydia ranging from 46 to 54% in young people with gonorrhoea. Among persons in the United States between 14 and 39 years of age, 46% of people with gonorrhoeal infection also have chlamydial infection. For this reason, gonorrhoea and chlamydia testing are often combined. People diagnosed with gonorrhoea infection have a fivefold increase risk of HIV transmission. Additionally, infected persons who are HIV positive are more likely to shed and transmit HIV to uninfected partners during an episode of gonorrhoea.

Antibiotics are used to treat gonorrhoea infections. As of 2016, both ceftriaxone by injection and azithromycin by mouth are most effective. However, due to increasing rates of antibiotic resistance, local susceptibility patterns must be taken into account when deciding on treatment.

Adults may have eyes infected with gonorrhoea and require proper personal hygiene and medications. Addition of topical antibiotics have not been shown to improve cure rates compared to oral antibiotics alone in treatment of eye infected gonorrhoea. For newborns, erythromycin ointment is recommended as a preventative measure for gonococcal infant conjunctivitis.

Infections of the throat can be especially problematic, as antibiotics have difficulty becoming sufficiently concentrated there to destroy the bacteria. This is amplified by the fact that pharyngeal gonorrhoea is mostly asymptomatic, and gonococci and commensal *Neisseria* species can coexist for long time periods in the pharynx and share anti-microbial resistance genes. Accordingly, an enhanced focus on early detection (i.e., screening of high-risk populations, such as men who have sex with men, PCR testing should be considered) and appropriate treatment of pharyngeal gonorrhoea is important.



## Sexual partners

It is recommended that sexual partners be tested and potentially treated. One option for treating sexual partners of people infected is patient-delivered partner therapy (PDPT), which involves providing prescriptions or medications to the person to take to his/her partner without the health care provider's first examining him/her.

The United States' Centers for Disease Control and Prevention (CDC) currently recommend that individuals who have been diagnosed and treated for gonorrhea avoid sexual contact with others until at least one week past the final day of treatment in order to prevent the spread of the bacterium.

Gonorrhea if left untreated may last for weeks or months with higher risks of complications.

One of the complications of gonorrhea is systemic dissemination resulting in skin pustules or petechia, septic arthritis, meningitis, or endocarditis. This occurs in between 0.6 and 3% of infected women and 0.4 and 0.7% of infected men.

In men, inflammation of the epididymis, prostate gland, and urethra can result from untreated gonorrhea. In women, the most common result of untreated gonorrhea is pelvic inflammatory disease. Other complications include inflammation of the tissue surrounding the liver, a rare complication associated with Fitz-Hugh–Curtis syndrome; septic arthritis in the fingers, wrists, toes, and ankles; septic abortion; chorioamnionitis during pregnancy; neonatal or adult blindness from conjunctivitis; and infertility. Men who have had a gonorrhea infection have an increased risk of getting prostate cancer.



## Hepatitis

Hepatitis is inflammation of the liver tissue. Some people or animals with hepatitis have no symptoms, whereas others develop yellow discoloration of the skin and whites of the eyes (jaundice), poor appetite, vomiting, tiredness, abdominal pain, and diarrhea. Hepatitis is acute if it resolves within six months, and chronic if it lasts longer than six months. Acute hepatitis can resolve on its own, progress to chronic hepatitis, or (rarely) result in acute liver failure. Chronic hepatitis may progress to scarring of the liver (cirrhosis), liver failure, and liver cancer.

Hepatitis is most commonly caused by the viruses hepatitis A, B, C, D, and E. Other causes include heavy alcohol use, certain medications, toxins, other infections, autoimmune diseases, and non-alcoholic steatohepatitis (NASH). Hepatitis A and E are mainly spread by contaminated food and water. Hepatitis B is mainly sexually transmitted, but may also be passed from mother to baby during pregnancy or childbirth and spread through infected blood. Hepatitis C is commonly spread through infected blood such as may occur during needle sharing by intravenous drug users. Hepatitis D can only infect people already infected with hepatitis B.

Hepatitis A, B, and D are preventable with immunization. Medications may be used to treat chronic viral hepatitis. Antiviral medications are recommended in all with chronic hepatitis C, except those with conditions that limit their life expectancy. There is no specific treatment for NASH; however, physical activity, a healthy diet, and weight loss are recommended. Autoimmune hepatitis may be treated with medications to suppress the immune system. A liver transplant may be an option in both acute and chronic liver failure.

Worldwide in 2015, hepatitis A occurred in about 114 million people, chronic hepatitis B affected about 343 million people and chronic hepatitis C about 142 million people. In the United States, NASH affects about 11 million people and alcoholic hepatitis affects about 5 million people. Hepatitis results in more than a million deaths a year, most of which occur indirectly from liver scarring or liver cancer. In the United States, hepatitis A is estimated to occur in about 2,500 people a year and results in about 75 deaths. The word is derived from resolve by this time, but people will develop an enlarged liver and right upper abdominal pain or discomfort. 10–20% of people will also experience an enlarged spleen, while some people will also experience a mild unintentional weight loss.

The recovery phase is characterized by resolution of the clinical symptoms of hepatitis with persistent elevations in liver lab values and potentially a persistently enlarged liver. All cases of hepatitis A and E are expected to fully resolve after 1–2 months. Most hepatitis B cases are also self-limiting and will resolve in 3–4 months. Few cases of hepatitis C will resolve completely.

Both drug-induced hepatitis and autoimmune hepatitis can present very similarly to acute viral hepatitis, with slight variations in symptoms depending on the cause. Cases of drug-induced hepatitis can manifest with systemic signs of an allergic reaction including rash, fever, serositis (inflammation of membranes lining certain organs), elevated eosinophils (a type of white blood cell), and suppression of bone marrow activity.

### Fulminant hepatitis

Fulminant hepatitis, or massive hepatic cell death, is a rare and life-threatening complication of acute hepatitis that can occur in cases of hepatitis B, D, and E, in addition to drug-induced and autoimmune hepatitis. The complication more frequently occurs in instances of hepatitis B and D co-infection at a rate of 2–20% and in pregnant women with hepatitis E at rate of 15–20% of cases. In addition to the signs of acute hepatitis, people can also demonstrate signs of coagulopathy (abnormal coagulation studies with easy bruising and bleeding) and encephalopathy (confusion, disorientation, and sleepiness). Mortality due to fulminant hepatitis is typically the result of various complications including cerebral edema, gastrointestinal bleeding, sepsis, respiratory failure, or kidney failure.

### Chronic hepatitis

Acute cases of hepatitis are seen to be resolved well within a six-month period. When hepatitis is continued for more than six months it is termed chronic hepatitis. Chronic hepatitis is often asymptomatic early in its course and is detected only by liver laboratory studies for screening purposes or to evaluate non-specific symptoms.



As the inflammation progresses, patients can develop constitutional symptoms similar to acute hepatitis, including fatigue, nausea, vomiting, poor appetite, and joint pain. Jaundice can occur as well, but much later in the disease process and is typically a sign of advanced disease. Chronic hepatitis interferes with hormonal functions of the liver which can result in acne, hirsutism (abnormal hair growth), and amenorrhea (lack of menstrual period) in women. Extensive damage and scarring of the liver over time defines cirrhosis, a condition in which the liver's ability to function is permanently impeded. This results in jaundice, weight loss, coagulopathy, ascites (abdominal fluid collection), and peripheral edema (leg swelling). Cirrhosis can lead to other life-threatening complications such as hepatic encephalopathy, esophageal varices, hepatorenal syndrome, and liver cancer.

Causes of hepatitis can be divided into the following major categories: infectious, metabolic, ischemic, autoimmune, genetic, and other. Infectious agents include viruses, bacteria, and parasites. Metabolic causes include prescription medications, toxins (most notably alcohol), and nonalcoholic fatty liver disease. Autoimmune and genetic causes of hepatitis involve genetic predispositions and tend to affect characteristic populations.

Viral hepatitis is the most common type of hepatitis worldwide, especially in Asia and Africa. Viral hepatitis is caused by five different viruses (hepatitis A, B, C, D, and E). Hepatitis A and hepatitis E behave similarly: they are both transmitted by the fecal-oral route, are more common in developing countries, and are self-limiting illnesses that do not lead to chronic hepatitis.

Hepatitis B, hepatitis C, and hepatitis D are transmitted when blood or mucous membranes are exposed to infected blood and body fluids, such as semen and vaginal secretions. Viral particles have also been found in saliva and breastmilk. However contrary to myths, kissing, sharing utensils, and breastfeeding do not lead to transmission unless these fluids are introduced into open sores or cuts. Many families who do not have safe drinking water or live in unhygienic homes have contracted hepatitis because saliva and blood droplets are often carried through the water and blood-borne illnesses spread quickly in unsanitary settings.

Hepatitis B and C can present either acutely or chronically. Hepatitis D is a defective virus that requires hepatitis B to replicate and is only found with hepatitis B co-infection. In adults, hepatitis B infection is most commonly self-limiting, with less than 5% progressing to chronic state, and 20 to 30% of those chronically infected developing cirrhosis or liver cancer. However, infection in infants and children frequently leads to chronic infection.

Unlike hepatitis B, most cases of hepatitis C lead to chronic infection. Hepatitis C is the second most common cause of cirrhosis in the US (second to alcoholic hepatitis). In the 1970s and 1980s, blood transfusions were a major factor in spreading hepatitis C virus. Since widespread screening of blood products for hepatitis C began in 1992, the risk of acquiring hepatitis C from a blood transfusion has decreased from approximately 10% in the 1970s to 1 in 2 million currently.

#### Parasitic hepatitis

Parasites can also infect the liver and activate the immune response, resulting in symptoms of acute hepatitis with increased serum IgE (though chronic hepatitis is possible with chronic infections). Of the protozoans, *Trypanosoma cruzi*, *Leishmania* species, and the malaria-causing *Plasmodium* species all can cause liver inflammation. Another protozoan, *Entamoeba histolytica*, causes hepatitis with distinct liver abscesses.

Of the worms, the cestode *Echinococcus granulosus*, also known as the dog tapeworm, infects the liver and forms characteristic hepatic hydatid cysts. The liver flukes *Fasciola hepatica* and *Clonorchis sinensis* live in the bile ducts and cause progressive hepatitis and liver fibrosis.

#### Bacterial hepatitis

Bacterial infection of the liver commonly results in pyogenic liver abscesses, acute hepatitis, or granulomatous (or chronic) liver disease. Pyogenic abscesses commonly involve enteric bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* and are composed of multiple bacteria up to 50% of the time. Acute hepatitis is caused by *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Bartonella henselae*, *Borrelia burgdorferi*, *salmonella* species, *brucella* species and *campylobacter* species. Chronic or granulomatous hepatitis is seen with



infection from mycobacteria species, *Tropheryma whipplei*, *Treponema pallidum*, *Coxiella burnetii*, and rickettsia species.

Excessive alcohol consumption is a significant cause of hepatitis and is the most common cause of cirrhosis in the U.S. Alcoholic hepatitis is within the spectrum of alcoholic liver disease.

This ranges in order of severity and reversibility from alcoholic steatosis (least severe, most reversible), alcoholic hepatitis, cirrhosis, and liver cancer (most severe, least reversible).

Hepatitis usually develops over years-long exposure to alcohol, occurring in 10 to 20% of alcoholics. The most important risk factors for the development of alcoholic hepatitis are quantity and duration of alcohol intake. Long-term alcohol intake in excess of 80 grams of alcohol a day in men and 40 grams a day in women is associated with development of alcoholic hepatitis (1 beer or 4 ounces of wine is equivalent to 12g of alcohol). Alcoholic hepatitis can vary from asymptomatic hepatomegaly (enlarged liver) to symptoms of acute or chronic hepatitis to liver failure.

#### Toxic and drug-induced hepatitis

Many chemical agents, including medications, industrial toxins, and herbal and dietary supplements, can cause hepatitis. The spectrum of drug-induced liver injury varies from acute hepatitis to chronic hepatitis to acute liver failure. Toxins and medications can cause liver injury through a variety of mechanisms, including direct cell damage, disruption of cell metabolism, and causing structural changes. Some drugs such as paracetamol exhibit predictable dose-dependent liver damage while others such as isoniazid cause idiosyncratic and unpredictable reactions that vary among individuals. There are wide variations in the mechanisms of liver injury and latency period from exposure to development of clinical illness.

Many types of drugs can cause liver injury, including the analgesic paracetamol; antibiotics such as isoniazid, nitrofurantoin, amoxicillin-clavulanate, erythromycin, and trimethoprim-sulfamethoxazole; anticonvulsants such as valproate and phenytoin; cholesterol-lowering statins; steroids such as oral contraceptives and anabolic steroids; and highly active anti-retroviral therapy used in the treatment of HIV/AIDS. Of these, amoxicillin-clavulanate is the most common cause of drug-induced liver injury, and paracetamol toxicity the most common cause of acute liver failure in the United States and Europe.

Herbal remedies and dietary supplements are another important cause of hepatitis; these are the most common causes of drug-induced hepatitis in Korea. The United-States-based Drug Induced Liver Injury Network linked more than 16% of cases of hepatotoxicity to herbal

and dietary supplements. In the United States, herbal and dietary supplements – unlike pharmaceutical drugs – are unregulated by the Food and Drug Administration. However, the National Institutes of Health maintains the LiverTox Archived 2019-07-24 at the Wayback Machine database for consumers to track all known prescription and non-prescription compounds associated with liver injury.

Exposure to other hepatotoxins can occur accidentally or intentionally through ingestion, inhalation, and skin absorption. The industrial toxin carbon tetrachloride and the wild mushroom *Amanita phalloides* are other known hepatotoxins.

Genetic causes of hepatitis include alpha-1-antitrypsin deficiency, hemochromatosis, and Wilson's disease. In alpha-1-antitrypsin deficiency, a co-dominant mutation in the gene for alpha-1 antitrypsin results in the abnormal accumulation of the mutant AAT protein within liver cells, leading to liver disease.

Hemochromatosis and Wilson's disease are both autosomal recessive diseases involving abnormal storage of minerals. In hemochromatosis, excess amounts of iron accumulate in multiple body sites, including the liver, which can lead to cirrhosis. In Wilson's disease, excess amounts of copper accumulate in the liver and brain, causing cirrhosis and dementia.

When the liver is involved, alpha-1-antitrypsin deficiency and Wilson's disease tend to present as hepatitis in the neonatal period or in childhood. Hemochromatosis typically presents in adulthood, with the onset of clinical disease usually after age 50.

Ischemic hepatitis (also known as shock liver) results from reduced blood flow to the liver as in shock, heart failure, or vascular insufficiency. The condition is most often associated with heart failure but can also be



caused by shock or sepsis. Blood testing of a person with ischemic hepatitis will show very high levels of transaminase enzymes (AST and ALT). The condition usually resolves if the underlying cause is treated successfully. Ischemic hepatitis rarely causes permanent liver damage.

### Viral hepatitis

The pathway by which hepatic viruses cause viral hepatitis is best understood in the case of hepatitis B and C. The viruses do not directly activate apoptosis (cell death). Rather, infection of liver cells activates the innate and adaptive arms of the immune system leading to an inflammatory response which causes cellular damage and death, including

viral-induced apoptosis via the induction of the death receptor-mediated signaling pathway. Depending on the strength of the immune response, the types of immune cells involved and the ability of the virus to evade the body's defense, infection can either lead to clearance (acute disease) or persistence (chronic disease) of the virus. The chronic presence of the virus within liver cells results in multiple waves of inflammation, injury and wound healing that over time lead to scarring or fibrosis and culminate in hepatocellular carcinoma.

Individuals with an impaired immune response are at greater risk of developing chronic infection. Natural killer cells are the primary drivers of the initial innate response and create a cytokine environment that results in the recruitment of CD4 T-helper and CD8 cytotoxic T-cells. Type I interferons are the cytokines that drive the antiviral response. In chronic

Hepatitis B and C, natural killer cell function is impaired.

The treatment of hepatitis varies according to the type, whether it is acute or chronic, and the severity of the disease.

**Activity:** Many people with hepatitis prefer bed rest, though it is not necessary to avoid all physical activity while recovering.

**Diet:** A high-calorie diet is recommended. Many people develop nausea and cannot tolerate food later in the day, so the bulk of intake may be concentrated in the earlier part of the day. In the acute phase of the disease, intravenous feeding may be needed if patients cannot tolerate food and have poor oral intake subsequent to nausea and vomiting.

**Drugs:** People with hepatitis should avoid taking drugs metabolized by the liver. Glucocorticoids are not recommended as a treatment option for acute viral hepatitis and may even cause harm, such as development of chronic hepatitis.

**Precautions:** Universal precautions should be observed. Isolation is usually not needed, except in cases of hepatitis A and E who have fecal incontinence, and in cases of hepatitis B and C who have uncontrolled bleeding.

Hepatitis A usually does not progress to a chronic state, and rarely requires hospitalization.

Treatment is supportive and includes such measures as providing intravenous (IV) hydration and maintaining adequate nutrition.

Rarely, people with the hepatitis A virus can rapidly develop liver failure, termed fulminant hepatic failure, especially the elderly and those who had a pre-existing liver disease, especially hepatitis C. Mortality risk factors include greater age and chronic hepatitis C. In these cases, more aggressive supportive therapy and liver transplant may be necessary.

In healthy patients, 95–99% recover with no long-lasting effects, and antiviral treatment is not warranted. Age and comorbid conditions can result in a more prolonged and severe illness. Certain patients warrant hospitalization, especially those who present with clinical signs of ascites, peripheral edema, and hepatic encephalopathy, and laboratory signs of hypoglycemia, prolonged prothrombin time, low serum albumin, and very high serum bilirubin.

In these rare, more severe acute cases, patients have been successfully treated with antiviral therapy similar to that used in cases of chronic hepatitis B, with nucleoside analogues such as entecavir or tenofovir. As there is a



dearth of clinical trial data and the drugs used to treat are prone to developing resistance, experts recommend reserving treatment for severe acute cases, not mild to moderate.

Chronic hepatitis B management aims to control viral replication, which is correlated with progression of disease. Seven drugs are approved in the United States:

Injectable interferon alpha was the first therapy approved for chronic hepatitis B. It has several side effects, most of which are reversible with removal of therapy, but it has been supplanted by newer treatments for this indication. These include long-acting interferon bound to polyethylene glycol (pegylated interferon) and the oral nucleoside analogues.

Pegylated interferon (PEG IFN) is dosed just once a week as a subcutaneous injection and is both more convenient and effective than standard interferon. Although it does not develop resistance as do many of the oral antivirals, it is poorly tolerated and requires close monitoring. PEG IFN is estimated to cost about \$18,000 per year in the United States, compared to \$2,500–8,700 for the oral medications; however, its treatment duration is 48 weeks as opposed to the oral antivirals, which require indefinite treatment for most patients (minimum 1 year). PEG IFN is not effective in patients with high levels of viral activity and cannot be used in immunosuppressed patients or those with cirrhosis.

Lamivudine was the first approved oral nucleoside analogue. While effective and potent, lamivudine has been replaced by newer, more potent treatments in the Western world and is no longer recommended as first-line treatment. However, it is still used in areas where newer agents either have not been approved or are too costly. Generally, the course of treatment is a minimum of one year with a minimum of six additional months of "consolidation therapy." Based on viral response, longer therapy may be required, and certain patients require indefinite long-term therapy.

Due to a less robust response in Asian patients, consolidation therapy is recommended to be extended to at least a year. All patients should be monitored for viral reactivation, which if identified, requires restarting treatment. Lamivudine is generally safe and well tolerated.

Many patients develop resistance, which is correlated with longer treatment duration. If this occurs, an additional antiviral is added. Lamivudine as a single treatment is contraindicated in patients coinfecting with HIV, as resistance develops rapidly, but it can be used as part of a multidrug regimen.

Adefovir dipivoxil, a nucleotide analogue, has been used to supplement lamivudine in patients who develop resistance, but is no longer recommended as first-line therapy.

Entecavir is safe, well tolerated, less prone to developing resistance, and the most potent of the existing hepatitis B antivirals; it is thus a first-line treatment choice. It is not recommended for lamivudine-resistant patients or as monotherapy in patients who are HIV positive.

Telbivudine is effective but not recommended as first-line treatment; as compared to entecavir, it is both less potent and more resistance prone.

Tenofovir is a nucleotide analogue and an antiretroviral drug that is also used to treat HIV infection. It is preferred to adefovir both in lamivudine-resistant patients and as initial treatment since it is both more potent and less likely to develop resistance.

First-line treatments currently used include PEG IFN, entecavir, and tenofovir, subject to patient and physician preference. Treatment initiation is guided by recommendations issued by The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) and is based on detectable viral levels, HBeAg positive or negative status, ALT levels, and in certain cases, family history of HCC and liver biopsy.

In patients with compensated cirrhosis, treatment is recommended regardless of HBeAg status or ALT level,



but recommendations differ regarding HBV DNA levels; AASLD recommends treating at DNA levels detectable above  $2 \times 10^3$  IU/mL; EASL and WHO recommend treating when HBV DNA levels are detectable at any level. In patients with decompensated cirrhosis, treatment and evaluation for liver transplantation are recommended in all cases if HBV DNA is detectable. Currently, multidrug treatment is not recommended in treatment of chronic HBV as it is no more effective in the long term than individual treatment with entecavir or tenofovir.

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) recommend antiviral treatment for all patients with chronic hepatitis C infection except for those with additional chronic medical conditions that limit their life expectancy.

Once it is acquired, persistence of the hepatitis C virus is the rule, resulting in chronic hepatitis C. The goal of treatment is prevention of hepatocellular carcinoma (HCC). The best way to reduce the long-term risk of HCC is to achieve sustained virological response (SVR). SVR is defined as an undetectable viral load at 12 weeks after treatment completion and indicates a cure.

Currently available treatments include indirect and direct acting antiviral drugs. The indirect acting antivirals include pegylated interferon (PEG IFN) and ribavirin (RBV), which in combination have historically been the basis of therapy for HCV. Duration of and response to these treatments varies based on genotype. These agents are poorly tolerated but are still used in some resource-poor areas. In high-resource countries, they have been supplanted by direct acting antiviral agents, which first appeared in 2011; these agents target proteins responsible for viral replication and include the following three classes:

NS3/4A protease inhibitors, including telaprevir, boceprevir, simeprevir, and others. NS5A inhibitors, including ledipasvir, daclatasvir, and others.

NS5B polymerase inhibitors, including sofosbuvir, dasabuvir, and others.

These drugs are used in various combinations, sometimes combined with ribavirin, based on the patient's genotype, delineated as genotypes 1–6. [106] Genotype 1 (GT1), which is the most prevalent genotype in the United States and around the world, can now be cured with a direct acting antiviral regimen. First-line therapy for GT1 is a combination of sofosbuvir and ledipasvir (SOF/LDV) for 12 weeks for most patients, including those with advanced fibrosis or cirrhosis.

Certain patients with early disease need only 8 weeks of treatment while those with advanced fibrosis or cirrhosis who have not responded to prior treatment require 24 weeks. Cost remains a major factor limiting access to these drugs, particularly in low-resource nations; the cost of the 12-week GT1 regimen (SOF/LDV) has been estimated at US\$94,500.

Hepatitis D is difficult to treat, and effective treatments are lacking. Interferon alpha has proven effective at inhibiting viral activity but only on a temporary basis.

Similar to hepatitis A, treatment of hepatitis E is supportive and includes rest and ensuring adequate nutrition and hydration. Hospitalization may be required for particularly severe cases or for pregnant women.



## Herpes

Herpes simplex is a viral infection caused by the herpes simplex virus. Infections are categorized based on the part of the body infected. Oral herpes involves the face or mouth. It may result in small blisters in groups often called cold sores or fever blisters or may just cause a sore throat.

Genital herpes, often simply known as herpes, may have minimal symptoms or form blisters that break open and result in small ulcers. These typically heal over two to four weeks.

Tingling or shooting pains may occur before the blisters appear. Herpes cycles between periods of active disease followed by periods without symptoms. The first episode is often more severe and may be associated with fever, muscle pains, swollen lymph nodes and headaches. Over time, episodes of active disease decrease in frequency and severity. Other disorders caused by herpes simplex include: herpetic whitlow when it involves the fingers, herpes of the eye, herpes infection of the brain, and neonatal herpes when it affects a newborn, among others.

There are two types of herpes simplex virus, type 1 (HSV-1) and type 2 (HSV-2). HSV-1 more commonly causes infections around the mouth while HSV-2 more commonly causes genital infections. They are transmitted by direct contact with body fluids or lesions of an infected individual. Transmission may still occur when symptoms are not present. Genital herpes is classified as a sexually transmitted infection. It may be spread to an infant during childbirth. After infection, the viruses are transported along sensory nerves to the nerve cell bodies, where they reside lifelong. Causes of recurrence may include: decreased immune function, stress, and sunlight exposure. Oral and genital herpes is usually diagnosed based on the presenting symptoms. The diagnosis may be confirmed by viral culture or detecting herpes DNA in fluid from blisters. Testing the blood for antibodies against the virus can confirm a previous infection but will be negative in new infections.

The most effective method of avoiding genital infections is by avoiding vaginal, oral, and anal sex. Condom use decreases the risk. Daily antiviral medication taken by someone who has the infection can also reduce spread. There is no available vaccine and once infected, there is no cure.

Paracetamol (acetaminophen) and topical lidocaine may be used to help with the symptoms.

Treatments with antiviral medication such as aciclovir or valaciclovir can lessen the severity of symptomatic episodes.

Worldwide rates of either HSV-1 or HSV-2 are between 60% and 95% in adults. HSV-1 is usually acquired during childhood. Rates of both increase as people age. Rates of HSV-1 are between 70% and 80% in populations of low socioeconomic status and 40% to 60% in populations of improved socioeconomic status. An estimated 536 million people worldwide

(16% of the population) were infected with HSV-2 as of 2003 with greater rates among women and those in the developing world. Most people with HSV-2 do not realize that they resemble genital herpes, including fungal infection, lichen planus, atopic dermatitis, and urethritis.

Laboratory testing is often used to confirm a diagnosis of genital herpes. Laboratory tests include culture of the virus, direct fluorescent antibody (DFA) studies to detect virus, skin biopsy, and polymerase chain reaction to test for presence of viral DNA. Although these procedures produce highly sensitive and specific diagnoses, their high costs and time constraints discourage their regular use in clinical practice.

Until the 1980s serological tests for antibodies to HSV were rarely useful to diagnosis and not routinely used in clinical practice. The older IgM serologic assay could not differentiate between antibodies generated in response to HSV-1 or HSV-2 infection. However, a glycoprotein G-specific (IgG) HSV test introduced in the 1980s is more than 98% specific at discriminating HSV-1 from HSV-2.

Differential diagnosis



It should not be confused with conditions caused by other viruses in the herpesviridae family such as herpes zoster, which is caused by varicella zoster virus. The differential diagnosis includes hand, foot and mouth disease due to similar lesions on the skin.

Lymphangioma circumscriptum and dermatitis herpetiformis may also have a similar appearance.

As with almost all sexually transmitted infections, women are more susceptible to acquiring genital HSV-2 than men. On an annual basis, without the use of antivirals or condoms, the transmission risk of HSV-2 from infected male to female is about 8–11%. This is believed to be due to the increased exposure of mucosal tissue to potential infection sites. Transmission risk from infected female to male is around 4–5% annually. Suppressive antiviral therapy reduces these risks by 50%. Antivirals also help prevent the development of symptomatic HSV in infection scenarios, meaning the infected partner will be seropositive but symptom-free by about 50%. Condom use also reduces the transmission risk significantly. Condom use is much more effective at preventing male-to-female transmission than vice versa. Previous HSV-1 infection may reduce the risk for acquisition of HSV-2 infection among women by a factor of three, although the one study that states this has a small sample size of 14 transmissions out of 214 couples.

However, asymptomatic carriers of the HSV-2 virus are still contagious. In many infections, the first symptom people will have of their own infections is the horizontal transmission to a sexual partner or the vertical transmission of neonatal herpes to a newborn at term. Since most asymptomatic individuals are unaware of their infection, they are considered at high risk for spreading HSV.

In October 2011, the anti-HIV drug tenofovir, when used topically in a microbicide vaginal gel, was reported to reduce herpes virus sexual transmission by 51%.

#### Barrier methods

Condoms offer moderate protection against HSV-2 in both men and women, with consistent condom users having a 30%-lower risk of HSV-2 acquisition compared with those who never use condoms. A female condom can provide greater protection than the male condom, as it covers the labia.

The virus cannot pass through a synthetic condom, but a male condom's effectiveness is limited because herpes ulcers may appear on areas not covered by it. Neither type of condom prevents contact with the scrotum, anus, buttocks, or upper thighs, areas that may come in contact with ulcers or genital secretions during sexual activity. Protection against herpes simplex depends on the site of the ulcer; therefore, if ulcers appear on areas not covered by condoms, abstaining from sexual activity until the ulcers are fully healed is one way to limit risk of transmission. The risk is not eliminated, however, as viral shedding capable of transmitting infection may still occur while the infected partner is asymptomatic. The use of condoms or dental dams also limits the transmission of herpes from the genitals of one partner to the mouth of the other (or vice versa) during oral sex. When one partner has a herpes simplex infection and the other does not, the use of antiviral medication, such as valaciclovir, in conjunction with a condom, further decreases the chances of transmission to the uninfected partner. Topical microbicides that contain chemicals that directly inactivate the virus and block viral entry are being investigated.

#### Antivirals

Antivirals may reduce asymptomatic shedding; asymptomatic genital HSV-2 viral shedding is believed to occur on 20% of days per year in patients not undergoing antiviral treatment, versus 10% of days while on antiviral therapy.

#### Pregnancy

The risk of transmission from mother to baby is highest if the mother becomes infected around the time of delivery (30% to 60%), since insufficient time will have occurred for the generation and transfer of protective maternal antibodies before the birth of the child. In contrast, the risk falls to 3% if the infection is recurrent, and is 1–3% if the woman is seropositive for both HSV-1 and HSV-2, and is less than 1% if no lesions are visible. Women seropositive for only one type of HSV are only half as likely to transmit HSV as infected



seronegative mothers. To prevent neonatal infections, seronegative women are recommended to avoid unprotected oral-genital contact with an HSV-1-seropositive partner and conventional sex with a partner having a genital infection during the last trimester of pregnancy. Mothers infected with HSV are advised to avoid procedures that would cause trauma to the infant during birth (e.g. fetal scalp electrodes, forceps, and vacuum extractors) and, should lesions be present, to elect caesarean section to reduce exposure of the child to infected secretions in the birth canal. The use of antiviral treatments, such as aciclovir, given from the 36th week of pregnancy, limits HSV recurrence and shedding during childbirth, thereby reducing the need for caesarean section.

Aciclovir is the recommended antiviral for herpes suppressive therapy during the last months of pregnancy. The use of valaciclovir and famciclovir, while potentially improving compliance, have less-well-determined safety in pregnancy.

No method eradicates herpes virus from the body, but antiviral medications can reduce the frequency, duration, and severity of outbreaks. Analgesics such as ibuprofen and paracetamol (acetaminophen) can reduce pain and fever. Topical anesthetic treatments such as prilocaine, lidocaine, benzocaine, or tetracaine can also relieve itching and pain.

## HIV & AIDS

Human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV), a retrovirus. Following initial infection an individual may not notice any symptoms,

or may experience a brief period of influenza-like illness. Typically, this is followed by a prolonged incubation period with no symptoms. If the infection progresses, it interferes more with the immune system, increasing the risk of developing common infections such as tuberculosis, as well as other opportunistic infections, and tumors which are otherwise rare in people who have normal immune function. These late symptoms of infection are referred to as acquired immunodeficiency syndrome (AIDS). This stage is often also associated with unintended weight loss.

HIV is spread primarily by unprotected sex (including anal and vaginal sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Some bodily fluids, such as saliva, sweat and tears, do not transmit the virus. Oral sex has little to no risk of transmitting the virus.

Methods of prevention include safe sex, needle exchange programs, treating those who are infected, as well as both pre- and post-exposure prophylaxis. Disease in a baby can often be prevented by giving both the mother and child antiretroviral medication.

Known as the Berlin Patient and the London Patient, two individuals have been reported cured of AIDS and the NIH and Gates Foundation pledged \$200 million focused on developing a global cure for AIDS. While there is not yet a broadly available cure or vaccine, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy.

Treatment is recommended as soon as the diagnosis is made. Without treatment, the average survival time after infection is 11 years.

In 2020, about 37 million people worldwide were living with HIV and 680,000 deaths had occurred in that year. An estimated 20.6 million of these live in eastern and southern Africa. Between the time that AIDS was identified (in the early 1980s) and 2020, the disease has caused an estimated 36 million deaths worldwide. HIV/AIDS is considered a pandemic—a disease outbreak which is present over a large area and is actively spreading.

HIV made the jump from other primates to humans in west-central Africa in the early-to-mid 20th century. AIDS was first recognized by the United States' Centers for Disease Control and Prevention (CDC) in 1981 and its cause—HIV infection—was identified in the early part of the decade.



HIV/AIDS has had a large impact on society, both as an illness and as a source of discrimination. The disease also has large economic impacts. There are many misconceptions about HIV/AIDS, such as the belief that it can be transmitted by casual non-sexual contact.

The disease has become subject to many controversies involving religion, including the Catholic Church's position not to support condom use as prevention. It has attracted international medical and political attention as well as large-scale funding since it was identified in the 1980s.

There are three main stages of HIV infection: acute infection, clinical latency, and AIDS.

The initial period following the contraction of HIV is called acute HIV, primary HIV or acute retroviral syndrome. Many individuals develop an influenza-like illness or a mononucleosis-like illness 2–4 weeks after exposure while others have no significant symptoms. Symptoms occur in 40–90% of cases and most commonly include fever, large tender lymph nodes, throat inflammation, a rash, headache, tiredness, and/or sores of the mouth and genitals. The rash, which occurs in 20–50% of cases, presents itself on the trunk and is maculopapular, classically. Some people also develop opportunistic infections at this stage. Gastrointestinal symptoms, such as vomiting or diarrhea may occur. Neurological symptoms of peripheral neuropathy or Guillain-Barré syndrome also occur. The duration of the symptoms varies, but is usually one or two weeks.

Owing to their nonspecific character, these symptoms are not often recognized as signs of HIV infection. Even cases that do get seen by a family doctor or a hospital are often misdiagnosed as one of the many common infectious diseases with overlapping symptoms. Thus, it is recommended that HIV be considered in people presenting with an unexplained fever who may have risk factors for the infection.

#### Clinical latency

The initial symptoms are followed by a stage called clinical latency, asymptomatic HIV, or chronic HIV. Without treatment, this second stage of the natural history of HIV infection can last from about three years to over 20 years (on average, about eight years). While typically there are few or no symptoms at first, near the end of this stage many people experience fever, weight loss, gastrointestinal problems and muscle pains. Between 50% and 70% of people also develop persistent generalized lymphadenopathy, characterized by unexplained, non-painful enlargement of more than one group of lymph nodes (other than in the groin) for over three to six months.

Although most HIV-1 infected individuals have a detectable viral load and in the absence of treatment will eventually progress to AIDS, a small proportion (about 5%) retain high levels of CD4+ T cells (T helper cells) without antiretroviral therapy for more than five years. These individuals are classified as "HIV controllers" or long-term nonprogressors (LTNP).

Another group consists of those who maintain a low or undetectable viral load without anti-retroviral treatment, known as "elite controllers" or "elite suppressors". They represent approximately 1 in 300 infected persons.

#### Main symptoms of AIDS.

Acquired immunodeficiency syndrome (AIDS) is defined as an HIV infection with either a CD4+ T cell count below 200 cells per  $\mu\text{L}$  or the occurrence of specific diseases associated with HIV infection. In the absence of specific treatment, around half of people infected with HIV develop AIDS within ten years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia (40%), cachexia in the form of HIV wasting syndrome (20%), and esophageal candidiasis. Other common signs include recurrent respiratory tract infections.

Opportunistic infections may be caused by bacteria, viruses, fungi, and parasites that are normally controlled by the immune system. Which infections occur depends partly on what organisms are common in the person's environment. These infections may affect nearly every organ system.



People with AIDS have an increased risk of developing various viral-induced cancers, including Kaposi's sarcoma, Burkitt's lymphoma, primary central nervous system lymphoma, and cervical cancer. Kaposi's sarcoma is the most common cancer, occurring in 10% to 20% of people with HIV. The second-most common cancer is lymphoma, which is the cause of death of nearly 16% of people with AIDS and is the initial sign of AIDS in 3% to 4%. Both these cancers are associated with human herpesvirus 8 (HHV-8). Cervical cancer occurs more frequently in those with AIDS because of its association with human papillomavirus (HPV). Conjunctival cancer (of the layer that lines the inner part of eyelids and the white part of the eye) is also more common in those with HIV.

Additionally, people with AIDS frequently have systemic symptoms such as prolonged fevers, sweats (particularly at night), swollen lymph nodes, chills, weakness, and unintended weight loss. Diarrhea is another common symptom, present in about 90% of people with AIDS.

They can also be affected by diverse psychiatric and neurological symptoms independent of opportunistic infections and cancers.

HIV is spread by three main routes: sexual contact, significant exposure to infected body fluids or tissues, and from mother to child during pregnancy, delivery, or breastfeeding (known as vertical transmission). There is no risk of acquiring HIV if exposed to feces, nasal secretions, saliva, sputum, sweat, tears, urine, or vomit unless these are contaminated with blood. It is also possible to be co-infected by more than one strain of HIV—a condition known as HIV superinfection.

The most frequent mode of transmission of HIV is through sexual contact with an infected person. However, an HIV-positive person who has an undetectable viral load as a result of long-term treatment has effectively no risk of transmitting HIV sexually. The existence of functionally noncontagious HIV-positive people on antiretroviral therapy was controversially publicized in the 2008 Swiss Statement, and has since become accepted as medically sound.

Globally, the most common mode of HIV transmission is via sexual contacts between people of the opposite sex; however, the pattern of transmission varies among countries. As of 2017, most HIV transmission in the United States occurred among men who had sex with men (82% of new HIV diagnoses among males aged 13 and older and 70% of total new diagnoses). In the US, gay and bisexual men aged 13 to 24 accounted for an estimated 92% of new HIV diagnoses among all men in their age group and 27% of new diagnoses among all gay and bisexual men.

With regard to unprotected heterosexual contacts, estimates of the risk of HIV transmission per sexual act appear to be four to ten times higher in low-income countries than in high-income countries.<sup>[60]</sup> In low-income countries, the risk of female-to-male transmission is estimated as 0.38% per act, and of male-to-female transmission as 0.30% per act; the equivalent estimates for high-income countries are 0.04% per act for female-to-male transmission, and 0.08% per act for male-to-female transmission. The risk of transmission from anal intercourse is especially high, estimated as 1.4–1.7% per act in both heterosexual and homosexual contacts. While the risk of transmission from oral sex is relatively low, it is still present. The risk from receiving oral sex has been described as "nearly nil"; however, a few cases have been reported. The per-act risk is estimated at 0–0.04% for receptive oral intercourse. In settings involving prostitution in low-income countries, risk of female-to-male transmission has been estimated as 2.4% per act, and of male-to-female transmission as 0.05% per act.

Risk of transmission increases in the presence of many sexually transmitted infections and genital ulcers. Genital ulcers appear to increase the risk approximately fivefold. Other sexually transmitted infections, such as gonorrhea, chlamydia, trichomoniasis, and bacterial vaginosis, are associated with somewhat smaller increases in risk of transmission.

The viral load of an infected person is an important risk factor in both sexual and mother-to-child transmission. During the first 2.5 months of an HIV infection a person's infectiousness is twelve times higher due to the high viral load associated with acute HIV. If the person is in the



late stages of infection, rates of transmission are approximately eightfold greater.

Commercial sex workers (including those in pornography) have an increased likelihood of contracting HIV. Rough sex can be a factor associated with an increased risk of transmission.

Sexual assault is also believed to carry an increased risk of HIV transmission as condoms are rarely worn, physical trauma to the vagina or rectum is likely, and there may be a greater risk of concurrent sexually transmitted infections.

**Body fluids** The second-most frequent mode of HIV transmission is via blood and blood products. Bloodborne transmission can be through needle-sharing during intravenous drug use, needle-stick injury, transfusion of contaminated blood or blood product, or medical injections with unsterilized equipment. The risk from sharing a needle during drug injection

is between 0.63% and 2.4% per act, with an average of 0.8%. The risk of acquiring HIV from a needle stick from an HIV-infected person is estimated as 0.3% (about 1 in 333) per act and the risk following mucous membrane exposure to infected blood as 0.09% (about 1 in 1000) per act.

This risk may, however, be up to 5% if the introduced blood was from a person with a high viral load and the cut was deep. In the United States intravenous drug users made up 12% of all new cases of HIV in 2009, and in some areas more than 80% of people who inject drugs are HIV-positive.

HIV is transmitted in about 90% of blood transfusions using infected blood. In developed countries the risk of acquiring HIV from a blood transfusion is extremely low (less than one in half a million) where improved donor selection and HIV screening is performed; for example, in the UK the risk is reported at one in five million and in the United States it was one in 1.5 million in 2008. In low-income countries, only half of transfusions may be appropriately screened (as of 2008), and it is estimated that up to 15% of HIV infections in these areas come from transfusion of infected blood and blood products, representing between 5% and 10% of global infections. It is possible to acquire HIV from organ and tissue transplantation, although this is rare because of screening.

Unsafe medical injections play a role in HIV spread in sub-Saharan Africa. In 2007, between 12% and 17% of infections in this region were attributed to medical syringe use. The World Health Organization estimates the risk of transmission as a result of a medical injection in Africa at 1.2%. Risks are also associated with invasive procedures, assisted delivery, and dental care in this area of the world.

People giving or receiving tattoos, piercings, and scarification are theoretically at risk of infection but no confirmed cases have been documented. It is not possible for mosquitoes or other insects to transmit HIV.

#### Mother-to-child

HIV can be transmitted from mother to child during pregnancy, during delivery, or through breast milk, resulting in the baby also contracting HIV. As of 2008, vertical transmission accounted for about 90% of cases of HIV in children. In the absence of treatment, the risk of transmission before or during birth is around 20%, and in those who also breastfeed 35%.

Treatment decreases this risk to less than 5%.

Antiretrovirals when taken by either the mother or the baby decrease the risk of transmission in those who do breastfeed. If blood contaminates food during pre-chewing it may pose a risk of transmission. If a woman is untreated, two years of breastfeeding results in an HIV/AIDS risk in her baby of about 17%. Due to the increased risk of death without breastfeeding in many areas in the developing world, the World Health Organization recommends either exclusive breastfeeding or the provision of safe formula. All women known to be HIV-positive should be taking lifelong antiretroviral therapy.

#### Prevention Sexual

contact

Consistent condom use reduces the risk of HIV transmission by approximately 80% over the long term.



When condoms are used consistently by a couple in which one person is infected, the rate of HIV infection is less than 1% per year. There is some evidence to suggest that female condoms may provide an equivalent level of protection. Application of avaginal gel containing tenofovir (a reverse transcriptase inhibitor) immediately before sex seems to reduce infection rates by approximately 40% among African women. By contrast, use of the spermicide nonoxynol-9 may increase the risk of transmission due to its tendency to cause vaginal and rectal irritation.

Circumcision in Sub-Saharan Africa "reduces the acquisition of HIV by heterosexual men by between 38% and 66% over 24 months". Owing to these studies, both the World Health Organization and UNAIDS recommended male circumcision in 2007 as a method of preventing female-to-male HIV transmission in areas with high rates of HIV. However, whether it protects against male-to-female transmission is disputed, and whether it is of benefit in developed countries and among men who have sex with men is undetermined.

Programs encouraging sexual abstinence do not appear to affect subsequent HIV risk. Evidence of any benefit from peer education is equally poor. Comprehensive sexual education provided at school may decrease high-risk behavior. A substantial minority of young people continues to engage in high-risk practices despite knowing about HIV/AIDS, underestimating their own risk of becoming infected with HIV. Voluntary counseling and testing people for HIV does not affect risky behavior in those who test negative but does increase condom use in those who test positive. Enhanced family planning services appear to increase the likelihood of women with HIV using contraception, compared to basic services. It is not known whether treating other sexually transmitted infections is effective in preventing HIV.

#### Pre-exposure

Antiretroviral treatment among people with HIV whose CD4 count  $\leq 550$  cells/ $\mu$ L is a very effective way to prevent HIV infection of their partner (a strategy known as treatment as prevention, or TASP). TASP is associated with a 10- to 20-fold reduction in transmission risk. Pre-exposure prophylaxis (PrEP) with a daily dose of the medications tenofovir, with or without emtricitabine, is effective in people at high risk including men who have sex with men, couples where one is HIV-positive, and young heterosexuals in Africa. It may also be effective in intravenous drug users, with a study finding a decrease in risk of 0.7 to 0.4 per 100 person years. The USPSTF, in 2019, recommended PrEP in those who are at high risk.

Universal precautions within the health care environment are believed to be effective in decreasing the risk of HIV. Intravenous drug use is an important risk factor, and harm reduction strategies such as needle-exchange programs and opioid substitution therapy appear effective in decreasing this risk.



## Post-exposure

A course of antiretrovirals administered within 48 to 72 hours after exposure to HIV-positive blood or genital secretions is referred to as post-exposure prophylaxis (PEP). The use of the single agent zidovudine reduces the risk of a HIV infection five-fold following a needle-stick injury.

As of 2013, the prevention regimen recommended in the United States consists of three medications—tenofovir, emtricitabine and raltegravir—as this may reduce the risk further.

PEP treatment is recommended after a sexual assault when the perpetrator is known to be HIV-positive, but is controversial when their HIV status is unknown. The duration of treatment is usually four weeks and is frequently associated with adverse effects—where zidovudine is used, about 70% of cases result in adverse effects such as nausea (24%), fatigue (22%), emotional distress (13%) and headaches (9%).

Programs to prevent the vertical transmission of HIV (from mothers to children) can reduce rates of transmission by 92–99%. This primarily involves the use of a combination of antiviral medications during pregnancy and after birth in the infant, and potentially includes bottle feeding rather than breastfeeding. If replacement feeding is acceptable, feasible, affordable, sustainable and safe, mothers should avoid breastfeeding their infants; however, exclusive breastfeeding is recommended during the first months of life if this is not the case. If exclusive breastfeeding is carried out, the provision of extended antiretroviral prophylaxis to the infant decreases the risk of transmission. In 2015, Cuba became the first country in the world to eradicate mother-to-child transmission of HIV.

There is currently no cure, nor an effective HIV vaccine. Treatment consists of highly active antiretroviral therapy (HAART), which slows progression of the disease. As of 2010, more than 6.6 million people were receiving HAART in low- and middle-income countries. Treatment also includes preventive and active treatment of opportunistic infections. As of March 2020, two people have been successfully cleared of HIV. Rapid initiation of antiretroviral therapy within one week of diagnosis appear to improve treatment outcomes in low and medium-income settings.

## Antiviral therapy

Stribild – a common once-daily ART regime consisting of elvitegravir, emtricitabine, tenofovir and the booster cobicistat.

The World Health Organization and the United States recommend antiretrovirals in people of all ages (including pregnant women) as soon as the diagnosis is made, regardless of CD4 count.

Once treatment is begun, it is recommended that it is continued without breaks or "holidays".

Many people are diagnosed only after treatment ideally should have begun. The desired outcome of treatment is a long-term plasma HIV-RNA count below 50 copies/mL. Levels to

determine if treatment is effective are initially recommended after four weeks and once levels fall below 50 copies/mL checks every three to six months are typically adequate. Inadequate control is deemed to be greater than 400 copies/mL. Based on these criteria treatment is effective in more than 95% of people during the first year.

Benefits of treatment include a decreased risk of progression to AIDS and a decreased risk of death. In the developing world, treatment also improves physical and mental health. With treatment, there is a 70% reduced risk of acquiring tuberculosis. Additional benefits include a decreased risk of transmission of the disease to sexual partners and a decrease in mother-to-child transmission. The effectiveness of treatment depends to a large part on compliance. Reasons for non-adherence to treatment include poor access to medical care, inadequate social supports, mental illness and drug abuse. The complexity of treatment regimens (due to pill numbers and dosing frequency) and adverse effects may reduce adherence. Even though cost is an important issue with some medications, 47% of those who needed them were taking them in low- and middle-income



countries as of 2010, and the rate of adherence is similar in low-income and high-income countries.

Specific adverse events are related to the antiretroviral agent taken. Some relatively common adverse events include: lipodystrophy syndrome, dyslipidemia, and diabetes mellitus, especially with protease inhibitors. Other common symptoms include diarrhea, and an increased risk of cardiovascular disease. Newer recommended treatments are associated with fewer adverse effects.

Certain medications may be associated with birth defects and therefore may be unsuitable for women hoping to have children.

Treatment recommendations for children are somewhat different from those for adults. The World Health Organization recommends treating all children less than five years of age; children above five are treated like adults. The United States guidelines recommend treating all children less than 12 months of age and all those with HIV RNA counts greater than 100,000 copies/mL between one year and five years of age.

The European Medicines Agency (EMA) has recommended the granting of marketing authorizations for two new antiretroviral (ARV) medicines, rilpivirine (Rekambys) and cabotegravir (Vocabria), to be used together for the treatment of people with human immunodeficiency virus type 1 (HIV-1) infection. The two medicines are the first ARVs that come in a long-acting injectable formulation. This means that instead of daily pills, people receive intramuscular injections monthly or every two months.

Current HAART options are combinations (or "cocktails") consisting of at least three medications belonging to at least two types, or "classes", of antiretroviral agents. Initially, treatment is typically a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside analog reverse transcriptase inhibitors (NRTIs). Typical NRTIs include: zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC). As of 2019, dolutegravir/lamivudine/tenofovir is listed by the World Health Organization as the first-line treatment for adults, with tenofovir/lamivudine/efavirenz as an alternative. Combinations of agents that include protease inhibitors (PI) are used if the above regimen loses effectiveness.

The combination of Rekambys and Vocabria injection is intended for maintenance treatment of adults who have undetectable HIV levels in the blood (viral load less than 50 copies/ml) with their current ARV treatment, and when the virus has not developed resistance to a certain class of anti-HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase strand transfer inhibitors (INIs).

Cabotegravir combined with rilpivirine (Cabenuva) is a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace a current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

Measures to prevent opportunistic infections are effective in many people with HIV/AIDS. In addition to improving current disease, treatment with antiretrovirals reduces the risk of developing additional opportunistic infections.

Adults and adolescents who are living with HIV (even on anti-retroviral therapy) with no evidence of active tuberculosis in settings with high tuberculosis burden should receive isoniazid preventive therapy (IPT); the tuberculin skin test can be used to help decide if IPT is needed.

Children with HIV may benefit from screening for tuberculosis. Vaccination against hepatitis A and B is advised for all people at risk of HIV before they become infected; however, it may also be given after infection.

Trimethoprim/sulfamethoxazole prophylaxis between four and six weeks of age, and ceasing breastfeeding of infants born to HIV-positive mothers, is recommended in resource-limited settings. It is also recommended to prevent PCP when a person's CD4 count is below 200 cells/uL and in those who have or have previously had PCP. People with substantial immunosuppression are also advised to receive prophylactic therapy for toxoplasmosis and MAC. Appropriate preventive measures reduced the rate of these infections by 50% between 1992 and 1997. Influenza vaccination and pneumococcal polysaccharide vaccine are often recommended in people with HIV/AIDS with some



evidence of benefit.

The World Health Organization (WHO) has issued recommendations regarding nutrient requirements in HIV/AIDS. A generally healthy diet is promoted. Dietary intake of micronutrients at RDA levels by HIV-infected adults is recommended by the WHO; higher intake of vitamin A, zinc, and iron can produce adverse effects in HIV-positive adults, and is not recommended unless there is documented deficiency. Dietary supplementation for people who are infected with HIV and who have inadequate nutrition or dietary deficiencies may strengthen their immune systems or help them recover from infections; however, evidence indicating an overall benefit in morbidity or reduction in mortality is not consistent.

Evidence for supplementation with selenium is mixed with some tentative evidence of benefit. For pregnant and lactating women with HIV, multivitamin supplement improves outcomes for both mothers and children. If the pregnant or lactating mother has been advised to take antiretroviral medication to prevent mother-to-child HIV transmission, multivitamin supplements should not replace these treatments.

There is some evidence that vitamin A supplementation in children with an HIV infection reduces mortality and improves growth.

#### Alternative medicine

In the US, approximately 60% of people with HIV use various forms of complementary or alternative medicine, whose effectiveness has not been established. There is not enough evidence to support the use of herbal medicines. There is insufficient evidence to recommend or support the use of medical cannabis to try to increase appetite or weight gain.



## Human Papillomavirus (HPV)

Human papillomavirus infection (HPV infection) is caused by a DNA virus from the Papillomaviridae family. Many HPV infections cause no symptoms and 90% resolve spontaneously within two years. However, in some cases, an HPV infection persists and results in either warts or precancerous lesions. These lesions, depending on the site affected, increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth, tonsils, or throat. Nearly all cervical cancer is due to HPV; two strains, HPV16 and HPV18, account for 70% of cases. HPV16 is responsible for almost 90% of HPV-positive oropharyngeal cancers. Between 60% and 90% of the other cancers listed above are also linked to HPV. HPV6 and HPV11 are common causes of genital warts and laryngeal papillomatosis.

An HPV infection is caused by human papillomavirus, a DNA virus from the papillomavirus family. Over 170 types have been described. More than 40 types may be spread through sexual contact and infect the anus and genitals. Risk factors for persistent infection by sexually transmitted types include early age of first sexual intercourse, multiple sexual partners, smoking, and poor immune function. These types are typically spread by sustained direct skin-to-skin contact, with vaginal and anal sex being the most common methods. Also, HPV infection can spread from a mother to baby during pregnancy. There is no evidence that HPV can spread via common items like toilet seats, but the types that cause warts may spread via surfaces such as floors. It has been found that patients with active genital HPV have shown to have HPV DNA on their finger tips. In addition, HPV is not killed by common hand sanitizers and disinfectants, so increasing the possibility of the virus being transferred via fomites. An individual can become infected with more than one type of HPV. HPV is only known to affect humans.

HPV vaccines can prevent the most common types of infection. To be most effective, inoculation should occur before the onset of sexual activity, and are therefore recommended between the ages of 9–13 years. Cervical cancer screening, such as the Papanicolaou test ("pap smear"), or examination of the cervix after applying acetic acid, can detect both early cancer and abnormal cells that may develop into cancer. Screening allows for early treatment which results in better outcomes. Screening has reduced both the number of cases and the number of deaths from cervical cancer. Genital warts can be removed by freezing.

Nearly every individual is infected by HPV at some point in their lives. HPV is the most common sexually transmitted infection (STI), globally. Worldwide in 2018, an estimated 569,000 new cases of cervical cancer occurred, with 311,000 deaths. Around 85% of these cervical cancers occurred in low- and middle-income countries. In the United States, about 30,700 cases of cancer due to HPV occur each year. Roughly, 1% of sexually active adults have genital warts.

Cases of skin warts have been described since the time of ancient Greece, while the fact that they are caused by a virus was not determined until 1907.

Some HPV types, such as HPV-5, may establish infections that persist for the lifetime of the individual without ever manifesting any clinical symptoms. HPV types 1 and 2 can cause common warts in some infected individuals. HPV types 6 and 11 can cause genital warts and laryngeal papillomatosis.

Skin infection ("cutaneous" infection) with HPV is very widespread. Skin infections with HPV can cause noncancerous skin growths called warts (verrucae). Warts are caused by a rapid growth of cells on the outer layer of the skin. While cases of warts have been described since the time of ancient Greece, their viral cause was not known until 1907.

Skin warts are most common in childhood and typically appear and regress spontaneously over the course of weeks to months. Recurring skin warts are common. All HPVs are believed to be capable of establishing long-term "latent" infections in small numbers of stem cells present in the skin. Although these latent



infections may never be fully eradicated, immunological control is thought to block the appearance of symptoms such as warts. Immunological control is HPV type-specific, meaning an individual may become resistant to one HPV type while remaining susceptible to other types.

Types of warts include:

Common warts are usually found on the hands and feet, but can also occur in other areas, such as the elbows or knees. Common warts have a characteristic cauliflower-like surface and are typically slightly raised above the surrounding skin. Cutaneous HPV types can cause genital warts but are not associated with the development of cancer.

Plantar warts are found on the soles of the feet; they grow inward, generally causing pain when walking.

Subungual or periungual warts form under the fingernail (subungual), around the fingernail, or on the cuticle (periungual). They are more difficult to treat than warts in other locations.

Flat warts are most commonly found on the arms, face, or forehead. Like common warts, flat warts occur most frequently in children and teens. In people with normal immune function, flat warts are not associated with the development of cancer.

Common, flat, and plantar warts are much less likely to spread from person to person. Genital warts

HPV infection of the skin in the genital area is the most common sexually transmitted infection worldwide. Such infections are associated with genital or anal warts (medically known as condylomata acuminata or venereal warts), and these warts are the most easily recognized sign of genital HPV infection.

The strains of HPV that can cause genital warts are usually different from those that cause warts on other parts of the body, such as the hands or feet, or even the inner thighs.

A wide variety of HPV types can cause genital warts, but types 6 and 11 together account for about 90% of all cases. However, in total more than 40 types of HPV are transmitted through sexual contact and can infect the skin of the anus and genitals. Such infections may cause genital warts, although they may also remain asymptomatic.

The great majority of genital HPV infections never cause any overt symptoms and are cleared by the immune system in a matter of months. Moreover, people may transmit the virus to others even if they do not display overt symptoms of infection. Most people acquire genital HPV infections at some point in their lives, and about 10% of women are currently infected. A large increase in the incidence of genital HPV infection occurs at the age when individuals begin to engage in sexual activity. As with cutaneous HPVs, immunity to genital HPV is believed to be specific to a specific strain of HPV.

Laryngeal papillomatosis

In addition to genital warts, infection by HPV types 6 and 11 can cause a rare condition known as recurrent laryngeal papillomatosis, in which warts form on the larynx or other areas of the respiratory tract. These warts can recur frequently, may interfere with breathing, and in extremely rare cases can progress to cancer. For these reasons, repeated surgery to remove the warts may be advisable.

HPV-induced cancers

About a dozen HPV types (including types 16, 18, 31, and 45) are called "high-risk" types because persistent infection has been linked to cancer of the oropharynx, larynx, vulva, vagina, cervix, penis, and anus. These cancers all involve sexually transmitted infection of HPV to the stratified epithelial tissue. Individuals infected with both HPV and HIV have an increased risk of developing cervical or anal cancer. HPV type 16 is the strain most likely to cause cancer and is present in about 47% of all cervical cancers, and in many vaginal and vulvar cancers, penile cancers, anal cancers, and cancers of the head and neck.



An estimated 561,200 new cancer cases worldwide (5.2% of all new cancers) were attributable to HPV in 2002, making HPV one of the most important infectious causes of cancer. HPV-associated cancers make up over 5% of total diagnosed cancer cases worldwide, and this incidence is higher in developing countries where it is estimated to cause almost half a million cases each year.

In the United States, about 30,700 cases of cancer due to HPV occur each year.

### Cancer development

Genome organization of human papillomavirus type 16, one of the subtypes known to cause cervical cancer (E1-E7 early genes, L1-L2 late genes: capsid) In some infected individuals, their immune systems may fail to control HPV. Lingering infection with high-risk HPV types, such as types 16, 18, 31, and 45, can favor the development of cancer. Co-factors such as cigarette smoke can also enhance the risk of such HPV-related cancers.

HPV is believed to cause cancer by integrating its genome into nuclear DNA. Some of the early genes expressed by HPV, such as E6 and E7, act as oncogenes that promote tumor growth and malignant transformation. HPV genome integration can also cause carcinogenesis by promoting genomic instability associated with alterations in DNA copy number.

E6 produces a protein (also called E6) that binds to and inactivates a protein in the host cell called p53. Normally, p53 acts to prevent cell growth, and promotes cell death in the presence of DNA damage. p53 also upregulates the p21 protein, which blocks the formation of the cyclin D/Cdk4 complex, thereby preventing the phosphorylation of retinoblastoma protein (RB), and in turn, halting cell cycle progression by preventing the activation of E2F. In short, p53 is a tumor suppressor protein that arrests the cell cycle and prevents cell growth and survival when DNA damage occurs. Thus, inactivation of p53 by E6 can promote unregulated cell division, cell growth, and cell survival, characteristics of cancer.

E6 also has a close relationship with the cellular protein E6-associated protein (E6-AP), which is involved in the ubiquitin ligase pathway, a system that acts to degrade proteins. E6-AP binds ubiquitin to the p53 protein, thereby flagging it for proteosomal degradation.

Studies have also shown a link between a wide range of HPV types and squamous cell carcinoma of the skin. In such cases, *in vitro* studies suggest that the E6 protein of the HPV virus may inhibit apoptosis induced by ultraviolet light.

### Cervical cancer

Nearly all cases of cervical cancer are associated with HPV infection, with two types, HPV16 and HPV18, present in 70% of cases. In 2012, twelve HPV types were considered carcinogenic for cervical cancer by the International Agency for Research on Cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV is necessary for cervical cancer to occur.

Persistent HPV infection increases the risk for developing cervical carcinoma. Individuals who have an increased incidence of these types of infection are women with HIV/AIDS, who are at a 22-fold increased risk of cervical cancer.

The carcinogenic HPV types in cervical cancer belong to the alpha papillomavirus genus and can be grouped further into HPV clades. The two major carcinogenic HPV clades, alpha papillomavirus-9 (A9) and alpha papillomavirus-7 (A7), contain HPV16 and HPV18, respectively.

These two HPV clades were shown to have different effects on tumour molecular characteristics and patient prognosis, with clade A7 being associated with more aggressive pathways and an inferior prognosis.

In 2012, about 528,000 new cases and 266,000 deaths from cervical cancer occurred worldwide. Around 85% of these occurred in the developing world.

Most HPV infections of the cervix are cleared rapidly by the immune system and do not progress to cervical



cancer. Because the process of transforming normal cervical cells into cancerous ones is slow, cancer occurs in people having been infected with HPV for a long time, usually over a decade or more (persistent infection). Furthermore, both the HPV infection and cervical cancer drive metabolic modifications that may be correlated with the

aberrant regulation of enzymes related to metabolic pathways.

Non-European (NE) HPV16 variants are significantly more carcinogenic than European (E) HPV16 variants.

#### Anal cancer

Studies show a link between HPV infection and anal cancers. Sexually transmitted HPVs are found in a large percentage of anal cancers. Moreover, the risk for anal cancer is 17 to 31 times higher among HIV-positive individuals who were coinfecting with high-risk HPV, and 80 times higher for particularly HIV-positive men who have sex with men.

Anal Pap smear screening for anal cancer might benefit some subpopulations of men or women engaging in anal sex. No consensus exists, though, that such screening is beneficial, or who should get an anal Pap smear.

#### Penile cancer

HPV is associated with approximately 50% of penile cancers. In the United States, penile cancer accounts for about 0.5% of all cancer cases in men. HPV16 is the most commonly associated type detected. The risk of penile cancer increases 2- to 3-fold for individuals who are infected with HIV as well as HPV.

#### Head and neck cancers

Oral infection with high-risk carcinogenic HPV types (most commonly HPV 16) is associated with an increasing number of head and neck cancers. This association is independent of tobacco and alcohol use.

Sexually transmitted forms of HPV account for about 25% of cancers of the mouth and upper throat (the oropharynx) worldwide, but the local percentage varies widely, from 70% in the United States to 4% in Brazil.

Engaging in anal or oral sex with an HPV-infected partner may increase the risk of developing these types of cancers.

In the United States, the number of newly diagnosed, HPV-associated head and neck cancers has surpassed that of cervical cancer cases. The rate of such cancers has increased from an estimated 0.8 cases per 100,000 people in 1988 to 4.5 per 100,000 in 2012, and, as of 2015, the rate has continued to increase. Researchers explain these recent data by an increase in oral sex. This type of cancer is more common in men than in women.

The mutational profile of HPV-positive and HPV-negative head and neck cancer has been reported, further demonstrating that they are fundamentally distinct diseases.

#### Lung cancer

Some evidence links HPV to benign and malignant tumors of the upper respiratory tract. The International Agency for Research on Cancer has found that people with lung cancer were significantly more likely to have several high-risk forms of HPV antibodies compared to those who did not have lung cancer. Researchers looking for HPV among 1,633 lung cancer patients and 2,729 people without the lung disease found that people with lung cancer had more types of HPV than noncancer patients did, and among lung cancer patients, the chances of having eight types of serious HPV were significantly increased. In addition, expression of HPV structural proteins by immunohistochemistry and in vitro studies suggest HPV presence in bronchial cancer and its precursor lesions. Another study detected HPV in the exhaled breath condensate (EBC), bronchial brushing and neoplastic lung tissue of cases, and found a presence of an HPV infection in 16.4% of the subjects affected by nonsmall cell lung cancer, but in none of the controls. The



reported average frequencies of HPV in lung cancers were 17% and 15% in Europe and the Americas, respectively, and the mean number of HPV in Asian lung cancer samples was 35.7%, with a considerable heterogeneity between certain countries and regions.

#### Skin cancer

In very rare cases, HPV may cause epidermodysplasia verruciformis (EV) in individuals with a weakened immune system. The virus, unchecked by the immune system, causes the overproduction of keratin by skin cells, resulting in lesions resembling warts or cutaneous horns which can ultimately transform into skin cancer, but the development is not well understood. The specific types of HPV that are associated with EV are HPV5, HPV8, and HPV14.

#### Transmission

Sexually transmitted HPV is divided into two categories: low-risk and high-risk. Low-risk HPVs cause warts on or around the genitals. Type 6 and 11 cause 90% of all genital warts and recurrent respiratory papillomatosis that causes benign tumors in the air passages.

High-risk HPVs cause cancer and consist of about a dozen identified types. Types 16 and 18 are responsible for causing most of HPV-caused cancers. These high-risk HPVs cause 5% of the cancers in the world. In the United States, high-risk HPVs cause 3% of all cancer cases in women and 2% in men.

Risk factors for persistent genital HPV infections, which increases the risk for developing cancer, include early age of first sexual intercourse, multiple partners, smoking, and immunosuppression. Genital HPV is spread by sustained direct skin-to-skin contact, with vaginal, anal, and oral sex being the most common methods. Occasionally it can spread from a mother to her baby during pregnancy. HPV is difficult to remove via standard hospital disinfection techniques, and may be transmitted in a healthcare setting on re-usable gynecological equipment, such as vaginal ultrasound transducers. The period of communicability is still unknown, but probably at least as long as visible HPV lesions persist. HPV may still be transmitted even after lesions are treated and no longer visible or present.

#### Perinatal

Although genital HPV types can be transmitted from mother to child during birth, the appearance of genital HPV-related diseases in newborns is rare. However, the lack of appearance does not rule out asymptomatic latent infection, as the virus has proven to be

capable of hiding for decades. Perinatal transmission of HPV types 6 and 11 can result in the development of juvenile onset recurrent respiratory papillomatosis (JORRP). JORRP is very rare, with rates of about 2 cases per 100,000 children in the United States. Although JORRP rates are substantially higher if a woman presents with genital warts at the time of giving birth, the risk of JORRP in such cases is still less than 1%.

#### Genital infections

Genital HPV infections are transmitted primarily by contact with the genitals, anus, or mouth of an infected sexual partner.

Of the 120 known human papilloma viruses, 51 species and three subtypes infect the genital mucosa. Fifteen are classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), three as probable high-risk (26, 53, and 66), and twelve as low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89).

Condoms do not completely protect from the virus because the areas around the genitals including the inner thigh area are not covered, thus exposing these areas to the infected person's skin.

#### Hands

Studies have shown HPV transmission between hands and genitals of the same person and sexual partners. Hernandez tested the genitals and dominant hand of each person in twenty-five heterosexual couples every other month for an average of seven months. She found two couples where the man's genitals infected



the woman's hand with high-risk HPV, two where her hand infected his genitals, one where her genitals infected his hand, two each where he infected his own hand, and she infected her own hand. Hands were not the main source of transmission in these twenty-five couples, but they were significant.

Partridge reports men's fingertips became positive for high risk HPV at more than half the rate (26% per two years) as their genitals (48%). Winer reports 14% of fingertip samples from sexually active women were positive.

Non-sexual hand contact seems to have little or no role in HPV transmission. Winer found all fourteen fingertip samples from virgin women negative at the start of her fingertip study. In a separate report on genital HPV infection, 1% of virgin women (1 of 76) with no sexual contact tested positive for HPV, while 10% of virgin women reporting non-penetrative sexual contact were positive (7 of 72).

#### Shared objects

Sharing of possibly contaminated objects, for example, razors, may transmit HPV. Although possible, transmission by routes other than sexual intercourse is less common for female genital HPV infection. Fingers-genital contact is a possible way of transmission but unlikely to be a significant source.

#### Blood

Though it has traditionally been assumed that HPV is not transmissible via blood—as it is thought to only infect cutaneous and mucosal tissues—recent studies have called this notion into question. Historically, HPV DNA has been detected in the blood of cervical cancer patients. In 2005, a group reported that, in frozen blood samples of 57 sexually naive pediatric patients who had vertical or transfusion-acquired HIV infection, (14.0%) of these samples also tested positive for HPV-16. This seems to indicate that it may be possible for HPV to be transmitted via blood transfusion. However, as non-sexual transmission of HPV by other means is not uncommon, this could not be definitively proven. In 2009, a group tested Australian Red Cross blood samples from 180 healthy male donors for HPV, and subsequently found DNA of one or more strains of the virus in 15 (8.3%) of the samples. However, it is important to note that detecting the presence of HPV DNA in blood is not the same as detecting the virus itself in blood, and whether or not the virus itself can or does reside in blood in infected individuals is still unknown.

As such, it remains to be determined whether HPV can or cannot be transmitted via blood. This is of concern, as blood donations are not currently screened for HPV, and at least some organizations such as the American Red Cross and other Red Cross societies do not presently appear to disallow HPV-positive individuals from donating blood.

#### Surgery

Hospital transmission of HPV, especially to surgical staff, has been documented. Surgeons, including urologists and/or anyone in the room, is subject to HPV infection by inhalation of noxious viral particles during electrocautery or laser ablation of a condyloma (wart). There has been a case report of a laser surgeon who developed extensive laryngeal papillomatosis after providing laser ablation to patients with anogenital condylomata.

Three vaccines are available to prevent infection by some HPV types: Gardasil, Gardasil 9 and Cervarix; all three protect against initial infection with HPV types 16 and 18, which cause most of the HPV-associated cancer cases. Gardasil also protects against HPV types 6 and 11, which cause 90% of genital warts. Gardasil is a recombinant quadrivalent vaccine, whereas Cervarix is bivalent, and is prepared from virus-like particles (VLP) of the L1 capsid protein. Gardasil 9 is nonavalent, it has the potential to prevent about 90% of cervical, vulvar, vaginal, and anal cancers. It can protect for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; the latter five cause up to 20% of cervical cancers which were not previously covered.

The vaccines provide little benefit to women already infected with HPV types 16 and 18. For this reason, the vaccine is recommended primarily for those women not yet having been exposed to HPV during sex. The



World Health Organization position paper on HPV vaccination clearly outlines appropriate, cost-effective strategies for using HPV vaccine in public sector programs.

There is high-certainty evidence that HPV vaccines protect against precancerous cervical lesions in young women, particularly those vaccinated aged 15 to 26. HPV vaccines do not increase the risk of serious adverse events. Longer follow-up is needed to monitor the impact of HPV vaccines on cervical cancer.

The CDC recommends the vaccines be delivered in two shots at an interval of least 6 months for those aged 11–12, and three doses for those 13 and older. In most /countries, they are funded only for female use, but are approved for male use in many countries, and

funded for teenage boys in Australia. The vaccine does not have any therapeutic effect on existing HPV infections or cervical lesions. In 2010, 49% of teenage girls in the US got the HPV vaccine.

Following studies suggesting that the vaccine is more effective in younger girls than in older teenagers, the United Kingdom, Switzerland, Mexico, the Netherlands and Quebec began offering the vaccine in a two-dose schedule for girls aged under 15 in 2014.

Cervical cancer screening recommendations have not changed for females who receive HPV vaccine. It remains a recommendation that women continue cervical screening, such as Pap smear testing, even after receiving the vaccine, since it does not prevent all types of cervical cancer.

Both men and women are carriers of HPV. The Gardasil vaccine also protects men against anal cancers and warts and genital warts.

Duration of both vaccines' efficacy has been observed since they were first developed, and is expected to be longlasting.

In December 2014, the FDA approved a nine-valent Gardasil-based vaccine, Gardasil 9, to protect against infection with the four strains of HPV covered by the first generation of Gardasil as well as five other strains responsible for 20% of cervical cancers (HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58).

There is currently no specific treatment for HPV infection. However, the viral infection is usually cleared to undetectable levels by the immune system. According to the Centers for Disease Control and Prevention, the body's immune system clears HPV naturally within two years for 90% of cases. However, experts do not agree on whether the virus is eliminated or reduced to undetectable levels, and it is difficult to know when it is contagious.

Follow up care is usually recommended and practiced by many health clinics. Follow-up is sometimes not successful because a portion of those treated do not return to be evaluated. In addition to the normal methods of phone calls and mail, text messaging and email can improve the number of people who return for care. As of 2015 it is unclear the best method of follow up following treatment of cervical intraepithelial neoplasia.



## **Pelvic Inflammatory Disease (PID)**

Pelvic inflammatory disease, also known as pelvic inflammatory disorder (PID), is an infection of the upper part of the female reproductive system, namely the uterus, fallopian tubes, and ovaries, and inside of the pelvis. Often, there may be no symptoms. Signs and symptoms, when present, may include lower abdominal pain, vaginal discharge, fever, burning with urination, pain with sex, bleeding after sex, or irregular menstruation. Untreated PID can result in long-term complications including infertility, ectopic pregnancy, chronic pelvic pain, and cancer.

The disease is caused by bacteria that spread from the vagina and cervix. Infections by *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are present in 75 to 90 percent of cases. Often, multiple different bacteria are involved. Without treatment, about 10 percent of those with a chlamydial infection and 40 percent of those with a gonorrhea infection will develop PID. Risk factors are generally similar to those of sexually transmitted infections and include a high number of sexual partners and drug use. Vaginal douching may also increase the risk. The diagnosis is typically based on the presenting signs and symptoms. It is recommended that the disease be considered in all women of childbearing age who have lower abdominal pain. A definitive diagnosis of PID is made by finding pus involving the fallopian tubes during surgery. Ultrasound may also be useful in diagnosis.

Efforts to prevent the disease include not having sex or having few sexual partners and using condoms. Screening women at risk for chlamydial infection followed by treatment decreases the risk of PID. If the diagnosis is suspected, treatment is typically advised. Treating a woman's sexual partners should also occur. In those with mild or moderate symptoms, a single injection of the antibiotic ceftriaxone along with two weeks of doxycycline and possibly metronidazole by mouth is recommended. For those who do not improve after three days or who have severe disease, intravenous antibiotics should be used.

Symptoms in PID range from none to severe. If there are symptoms, fever, cervical motion tenderness, lower abdominal pain, new or different discharge, painful intercourse, uterine tenderness, adnexal tenderness, or irregular menstruation may be noted.

Other complications include endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis, periappendicitis, and perihepatitis.

Globally, about 106 million cases of chlamydia and 106 million cases of gonorrhea occurred in 2008. The number of cases of PID, however, is not clear. It is estimated to affect about 1.5 percent of young women yearly. In the United States, PID is estimated to affect about one million people each year. A type of intrauterine device (IUD) known as the Dalkonshield led to increased rates of PID in the 1970s. Current IUDs are not associated with this problem after the first month.

PID can cause scarring inside the reproductive system, which can later cause serious complications, including chronic pelvic pain, infertility, ectopic pregnancy (the leading cause of pregnancy-related deaths in adult females), and other complications of pregnancy.

Occasionally, the infection can spread to the peritoneum causing inflammation and the formation of scar tissue on the external surface of the liver (Fitz-Hugh-Curtis syndrome).

*Chlamydia trachomatis* and *Neisseria gonorrhoeae* are usually the main cause of PID. Data suggest that PID is often polymicrobial. Isolated anaerobes and facultative microorganisms have been obtained from the upper genital tract. *N. gonorrhoeae* has been isolated from fallopian tubes, facultative and anaerobic organisms



were recovered from endometrial tissues.

The anatomical structure of the internal organs and tissues of the female reproductive tract provides a pathway for pathogens to ascend from the vagina to the pelvic cavity through the infundibulum. The disturbance of the naturally occurring vaginal microbiota associated with bacterial vaginosis increases the risk of PID.

*N. gonorrhoea* and *C. trachomatis* are the most common organisms. The least common were infections caused exclusively by anaerobes and facultative organisms. Anaerobes and facultative bacteria were also isolated from 50 percent of the patients from whom *Chlamydia* and *Neisseria* were recovered; thus, anaerobes and facultative bacteria were present in the upper genital tract of nearly two-thirds of the PID patients. PCR and serological tests have associated extremely fastidious organism with endometritis, PID, and tubal factor infertility. Microorganisms associated with PID are listed below.

Rarely cases of PID have developed in people who have stated they have never had sex.

Regular testing for sexually transmitted infections is encouraged for prevention. The risk of contracting pelvic inflammatory disease can be reduced by the following:

Using barrier methods such as condoms;

Seeking medical attention if you are experiencing symptoms of PID.

Using hormonal combined contraceptive pills also helps in reducing the chances of PID by thickening the cervical mucosal plug & hence preventing the ascent of causative organisms from the lower genital tract.

Seeking medical attention after learning that a current or former sex partner has, or might have had a sexually transmitted infection.

Getting a STI history from your current partner and strongly encouraging they be tested and treated before intercourse.

Diligence in avoiding vaginal activity, particularly intercourse, after the end of a pregnancy (delivery, miscarriage, or abortion) or certain gynecological procedures, to ensure that the cervix closes.

Reducing the number of sexual partners. Sexual

monogamy.

Abstinence.

Treatment is often started without confirmation of infection because of the serious complications that may result from delayed treatment. Treatment depends on the infectious agent and generally involves the use of antibiotic therapy although there is no clear evidence of which antibiotic regimen is more effective and safe in the management of PID. If there is no improvement within two to three days, the patient is typically advised to seek further medical attention. Hospitalization sometimes becomes necessary if there are other complications. Treating sexual partners for possible STIs can help in treatment and prevention.

For women with PID of mild to moderate severity, parenteral and oral therapies appear to be effective. It does not matter to their short- or long-term outcome whether antibiotics are administered to them as inpatients or outpatients. Typical regimens include cefoxitin or cefotetan plus doxycycline, and clindamycin plus gentamicin. An alternative parenteral regimen is ampicillin/sulbactam plus doxycycline. Erythromycin-based medications can also be used. A single study suggests superiority of azithromycin over doxycycline. Another alternative is to use a parenteral regimen with ceftriaxone or cefoxitin plus doxycycline. Clinical experience guides decisions regarding transition from parenteral to oral therapy, which usually can be initiated within 24–48 hours of clinical improvement.



## Syphilis

Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum* subspecies *pallidum*. The signs and symptoms of syphilis vary depending in which of the four stages it presents (primary, secondary, latent, and tertiary). The primary stage classically presents with a single chancre (a firm, painless, non-itchy skin ulceration usually between 1 cm and 2 cm in diameter) though there may be multiple sores. In secondary syphilis, a diffuse rash occurs, which frequently involves the palms of the hands and soles of the feet. There may also be sores in the mouth or vagina. In latent syphilis, which can last for years, there are few or no symptoms. In tertiary syphilis, there are gummas (soft, non-cancerous growths), neurological problems, or heart symptoms. Syphilis has been known as "the great imitator" as it may cause symptoms similar to many other diseases.

Syphilis is most commonly spread through sexual activity. It may also be transmitted from mother to baby during pregnancy or at birth, resulting in congenital syphilis. Other diseases caused by *Treponema* bacteria include yaws (*T. pallidum* subspecies *pertenue*), pinta (*T. carateum*), and nonvenereal endemic syphilis (*T. pallidum* subspecies *endemicum*). These three diseases are not typically sexually transmitted. Diagnosis is usually made by using blood tests; the bacteria can also be detected using dark field microscopy. The Centers for Disease Control and Prevention (U.S.) recommend all pregnant women be tested.

The risk of sexual transmission of syphilis can be reduced by using a latex or polyurethane condom. Syphilis can be effectively treated with antibiotics. The preferred antibiotic for most cases is benzathine benzylpenicillin injected into a muscle. In those who have a severe penicillin allergy, doxycycline or tetracycline may be used. In those with neurosyphilis, intravenous benzylpenicillin or ceftriaxone is recommended. During treatment people may develop fever, headache, and muscle pains, a reaction known as Jarisch–Herxheimer.

In 2015, about 45.4 million people had syphilis infections, of which six million were new cases. During 2015, it caused about 107,000 deaths, down from 202,000 in 1990. After decreasing dramatically with the availability of penicillin in the 1940s, rates of infection have increased since the turn of the millennium in many countries, often in combination with human immunodeficiency virus (HIV). This is believed to be partly due to increased promiscuity, prostitution, decreasing use of condoms and unsafe sexual practices among men who have sex with men.

Syphilis can present in one of four different stages: primary, secondary, latent, and tertiary, and may also occur congenitally. It was referred to as "the great imitator" by Sir William Osler due to its varied presentations.

### Primary

Primary syphilis is typically acquired by direct sexual contact with the infectious lesions of another person. Approximately 2–6 weeks after contact (with a range of 10–90 days) a skin lesion, called a chancre, appears at the site and this contains infectious spirochetes.

This is classically (40% of the time) a single, firm, painless, non-itchy skin ulceration with a clean base and sharp borders approximately 0.3–3.0 cm in size. The lesion may take on almost any form. In the classic form, it evolves from a macule to a papule and finally to an erosion or ulcer. Occasionally, multiple lesions may be present (~40%), with multiple lesions being more common when coinfecting with HIV. Lesions may be painful or tender (30%), and they may occur in places other than the genitals (2–7%). The most common location in women is the cervix (44%), the penis in heterosexual men (99%), and anally and rectally in men who have sex with men (34%). Lymph node enlargement frequently (80%) occurs around the area of infection, occurring seven to 10 days after chancre formation. The lesion may persist for three to six weeks if left untreated.

### Secondary

Secondary syphilis occurs approximately four to ten weeks after the primary infection. While secondary



disease is known for the many different ways it can manifest, symptoms most commonly involve the skin, mucous membranes, and lymph nodes. There may be a symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, including the palms and soles. The rash may become maculopapular or pustular. It may form flat, broad, whitish, wart-like lesions on mucous membranes, known as condyloma latum. All of these lesions harbor bacteria and are infectious. Other symptoms may include fever, sore throat, malaise, weight loss, hair loss, and headache. Rare manifestations include liver inflammation, kidney disease, joint inflammation, periostitis, inflammation of the optic nerve, uveitis, and interstitial keratitis. The acute symptoms usually resolve after three to six weeks; about 25% of people may present with a recurrence of secondary symptoms. Many people who present with secondary syphilis (40–85% of women, 20–65% of men) do not report previously having had the classical chancre of primary syphilis.

#### Latent

Latent syphilis is defined as having serologic proof of infection without symptoms of disease.

It develops after secondary syphilis and is divided into early latent and late latent stages. Early latent syphilis is defined by the World Health Organization as less than 2 years after original infection. Early latent syphilis is infectious as up to 25% of people can develop a recurrent secondary infection (during which spirochetes are actively replicating and are infectious). Two years after the original infection the person will enter late latent syphilis and is not as infectious as the early phase. The latent phase of syphilis can last many years after which, without treatment, approximately 15–40% of people can develop tertiary syphilis.

#### Tertiary

Tertiary syphilis may occur approximately 3 to 15 years after the initial infection, and may be divided into three different forms: gummatous syphilis (15%), late neurosyphilis (6.5%), and cardiovascular syphilis (10%). Without treatment, a third of infected people develop tertiary disease.

People with tertiary syphilis are not infectious.

Gummatous syphilis or late benign syphilis usually occurs 1 to 46 years after the initial infection, with an average of 15 years. This stage is characterized by the formation of chronic gummas, which are soft, tumor-like balls of inflammation which may vary considerably in size. They typically affect the skin, bone, and liver, but can occur anywhere.

Cardiovascular syphilis usually occurs 10–30 years after the initial infection. The most common complication is syphilitic aortitis, which may result in aortic aneurysm formation.

Neurosyphilis refers to an infection involving the central nervous system. Involvement of the central nervous system in syphilis (either asymptomatic or symptomatic) can occur at any stage of the infection. It may occur early, being either asymptomatic or in the form of syphilitic meningitis, or late as meningovascular syphilis, general paresis, or tabes dorsalis.

Meningovascular syphilis involves inflammation of the small and medium arteries of the central nervous system. It can present between 1–10 years after the initial infection. Meningovascular syphilis is characterized by stroke, cranial nerve palsies and spinal cord inflammation. Late symptomatic neurosyphilis can develop decades after the original infection and includes 2 types; general paresis and tabes dorsalis. General paresis presents with dementia, personality changes, delusions, seizures, psychosis and depression. Tabes dorsalis is characterized by gait instability, sharp pains in the trunk and limbs, impaired positional sensation of the limbs as well as having a positive Romberg's sign. Both tabes dorsalis and general paresis may present with Argyll Robertson pupil which are pupils that constrict when the person focuses on near objects (accommodation reflex) but do not constrict when exposed to bright light (pupillary reflex).

#### Congenital

Congenital syphilis is that which is transmitted during pregnancy or during birth. Two-thirds of syphilitic infants are born without symptoms. Common symptoms that develop over the first couple of years of life include enlargement of the liver and spleen (70%), rash (70%), fever (40%), neurosyphilis



(20%), and lung inflammation (20%). If untreated, late congenital syphilis may occur in 40%, including saddle nose deformation, Higouménakis' sign, saber shin, or Clutton's joints among others. Infection during pregnancy is also associated with miscarriage. The three main dental defects in congenital syphilis are Hutchinson's incisors (screwdriver shaped incisors), Moon's molars or bud molars, and Fournier's molars or mulberry molars (molars with abnormal occlusal anatomy resembling a mulberry).

## Treatment

Traditional mercury-based pastes were used in cures. Whilst this was partially effective, the toxic side effects of the mercury probably outweighed any advantages.

### Early infections

The first-line treatment for uncomplicated syphilis (primary or secondary stages) remains a single dose of intramuscular benzathine benzylpenicillin. Doxycycline and tetracycline are alternative choices for those allergic to penicillin; due to the risk of birth defects, these are not recommended for pregnant women. Resistance to macrolides, rifampicin, and clindamycin is often present. Ceftriaxone, a third-generation cephalosporin antibiotic, may be as effective as penicillin-based treatment. It is recommended that a treated person avoid sex until the sores are healed.

### Late infections

For neurosyphilis, due to the poor penetration of benzathine penicillin into the central nervous system, those affected are given large doses of intravenous penicillin G for a minimum of 10 days. If a person is allergic to penicillin, ceftriaxone may be used or penicillin desensitization attempted. Other late presentations may be treated with once-weekly intramuscular benzathine penicillin for three weeks. Treatment at this stage solely limits further progression of the disease and has a limited effect on damage which has already occurred. Serologic cure can be measured when the non-treponemal titers decline by a factor of 4 or more in 6–12 months in early syphilis or 12–24 months in late syphilis.



## Trichomoniasis

Trichomoniasis (trich) is an infectious disease caused by the parasite *Trichomonas vaginalis*.

About 70% of affected people do not have symptoms when infected. When symptoms occur, they typically begin 5 to 28 days after exposure. Symptoms can include itching in the genital area, a bad smelling thin vaginal discharge, burning with urination, and pain with sex. Having trichomoniasis increases the risk of getting HIV/AIDS. It may also cause complications during pregnancy.

Trichomoniasis is a sexually transmitted infection (STI) which is most often spread through vaginal, oral, or anal sex. It can also spread through genital touching. People who are infected may spread the disease even when symptoms are not present. Diagnosis is by finding the parasite in the vaginal fluid using a microscope, culturing the vaginal fluid or urine, or testing for the parasite's DNA. If present, other STIs should be tested for.

Methods of prevention include not having sex, using condoms, not douching, and being tested for STIs before having sex with a new partner. Although not caused by a bacteria, trichomoniasis can be cured with certain antibiotics (metronidazole, tinidazole, secnidazole). Sexual partners should also be treated. About 20% of people get infected again within three months of treatment.

There were about 122 million new cases of trichomoniasis in 2015. In the United States, there are about 2 million women affected. It occurs more often in women than men.

*Trichomonas vaginalis* was first identified in 1836 by Alfred Donné. It was first recognized as causing this disease in 1916.

Most people infected with *Trichomonas vaginalis* do not have any symptoms and can be undetected for years. Symptoms experienced include pain, burning or itching in the penis, urethra (urethritis), or vagina (vaginitis). Discomfort for both sexes may increase during intercourse and urination. For women there may also be a yellow-green, itchy, frothy, foul-smelling ("fishy"

smell) vaginal discharge. In rare cases, lower abdominal pain can occur. Symptoms usually appear within 5 to 28 days of exposure. Sometimes trichomoniasis can be confused with chlamydia because the symptoms are similar.

Trichomoniasis is linked to several serious complications.

Trichomoniasis is associated with increased risk of transmission and infection of HIV. Trichomoniasis may cause a woman to deliver a low-birth-weight or premature infant.

The role of *Trichomonas* infection in causing cervical cancer is unclear, although trichomonas infection may be associated with co-infection with high-risk strains of HPV.

*T. vaginalis* infection in males has been found to cause asymptomatic urethritis and prostatitis.

In the prostate, it may create chronic inflammation that may eventually lead to prostate cancer.

The human genital tract is the only reservoir for this species. *Trichomonas* is transmitted through sexual or genital contact.

The single-celled protozoan produces mechanical stress on host cells and then ingests cell fragments after cell death.



## Genetic sequence

A draft sequence of the *Trichomonas* genome was published on January 12, 2007, in the journal *Science* confirming that the genome has at least 26,000 genes, a similar number to the human genome. An additional approximately 34,000 unconfirmed genes, including thousands that are part of potentially transposable elements, brings the gene content to well over 60,000.

Use of male condoms or female condoms may help prevent the spread of trichomoniasis, although careful studies have never been done that focus on how to prevent this infection. Infection with trichomoniasis through water is unlikely because *Trichomonas vaginalis* dies in water after 45–60 minutes, in thermal water after 30 minutes to 3 hours and in diluted urine after 5–6 hours.

Currently there are no routine standard screening requirements for the general U.S. population receiving family planning or STI testing. The Centers for Disease Control and Prevention (CDC) recommends trichomoniasis testing for females with vaginal discharge and can be considered for females at higher risk for infection or of HIV-positive serostatus.

The advent of new, highly specific and sensitive trichomoniasis tests present opportunities for new screening protocols for both men and women. Careful planning, discussion, and research are required to determine the cost-efficiency and most beneficial use of these new tests for the diagnosis and treatment of trichomoniasis in the U.S., which can lead to better prevention efforts.

A number of strategies have been found to improve follow-up for STI testing including email and text messaging as reminders of appointments.

Treatment for both pregnant and non-pregnant women is usually with metronidazole, by mouth once. Caution should be used in pregnancy, especially in the first trimester. Sexual partners, even if they have no symptoms, should also be treated. Single oral dose of nitroimidazole is sufficient to kill the parasites.

For 95–97% of cases, infection is resolved after one dose of metronidazole. Studies suggest that 4–5% of trichomonas cases are resistant to metronidazole, which may account for some "repeat" cases. Without treatment, trichomoniasis can persist for months to years in women, and is thought to improve without treatment in men. Women living with HIV infection have better cure rates if treated for seven days rather than with one dose.

Topical treatments are less effective than oral antibiotics due to Skene's gland and other genitourinary structures acting as a reservoir.



## Chancroid

Chancroid (/ˈʃæŋkrɔɪd/ SHANG-kroyd) is a bacterial sexually transmitted infection characterized by painful sores on the genitalia. Chancroid is known to spread from one individual to another solely through sexual contact. However, there have been reports of accidental infection through another route which is by the hand. While uncommon in the western world, it is the most common cause of genital ulceration worldwide.

### Signs and symptoms

These are only local and no systemic manifestations are present. The ulcer characteristically:

Ranges in size dramatically from 3 to 50 mm (1/8 inch to two inches) across. Is painful.

Has sharply defined, undermined borders.

Has irregular or ragged borders, described as saucer-shaped. Has a base that is covered with a gray or yellowish-gray material. Has a base that bleeds easily if traumatized or scraped.

Painful swollen lymph nodes occurs in 30 to 60% of patients.

Dysuria (pain with urination) and dyspareunia (pain with intercourse) in females.

About half of infected men have only a single ulcer. Women frequently have four or more ulcers, with fewer symptoms. The ulcers are typically confined to the genital region most of the time.

The initial ulcer may be mistaken as a "hard" chancre, the typical sore of primary syphilis, as opposed to the "soft chancre" of chancroid.

Approximately one-third of the infected individuals will develop enlargements of the inguinal lymph nodes, the nodes located in the fold between the leg and the lower abdomen.

Half of those who develop swelling of the inguinal lymph nodes will progress to a point where the nodes rupture through the skin, producing draining abscesses. The swollen lymph nodes and abscesses are often referred to as buboes.

### Complications

Extensive lymph node inflammation may develop.

Large inguinal abscesses may develop and rupture to form draining sinus or giant ulcer.

Superinfection by *Fusarium* and *Bacteroides*. These later require debridement and may result in disfiguring scars.

Phimosis can develop in long-standing lesion by scarring and thickening of foreskin, which may subsequently require circumcision.

Chancroid spreads in populations with high sexual activity, such as prostitutes. Use of condom, prophylaxis by azithromycin, syndromic management of genital ulcers, treating patients with reactive syphilis serology are some of the strategies successfully tried in Thailand. Also, treatment of sexual partners is advocated whether they develop symptoms or not as long as there was unprotected sexual intercourse with the patient within 10



days of developing the symptoms.

For the initial stages of the lesion, cleaning with soapy solution is recommended and sitz bath may be beneficial. Fluctuant nodules may require aspiration. Treatment may include more than one prescribed medication.

#### Antibiotics

Macrolides are often used to treat chancroid. The CDC recommendation is either a single oral dose (1 gram) of azithromycin, a single IM dose (250 mg) of ceftriaxone, oral (500 mg) of erythromycin three times a day for seven days, or oral (500 mg) of ciprofloxacin twice a day for three days. Due to a paucity of reliable empirical evidence it is not clear whether macrolides are actually more effective and/or better tolerated than other antibiotics when treating chancroid. Data is limited, but there have been reports of ciprofloxacin and erythromycin resistance.

Aminoglycosides such as gentamicin, streptomycin, and kanamycin have been used to successfully treat chancroid; however aminoglycoside-resistant strain of *H. ducreyi* have been observed in both laboratory and clinical settings. Treatment with aminoglycosides should be considered as only a supplement to a primary treatment.

Pregnant and lactating women, or those below 18 years of age regardless of gender, should not use ciprofloxacin as treatment for chancroid. Treatment failure is possible with HIV co-infection and extended therapy is sometimes required.



## Lymphogranuloma Venereum (LGV)

Lymphogranuloma venereum (LGV; also known as climatic bubo Durand–Nicolas–Favre disease, poradenitis inguinale, lymphogranuloma inguinale, and strumous bubo) is a sexually transmitted disease caused by the invasive serovars L1, L2, L2a, L2b, or L3 of *Chlamydia trachomatis*.

LGV is primarily an infection of lymphatics and lymph nodes. *Chlamydia trachomatis* is the bacteria responsible for LGV. It gains entrance through breaks in the skin, or it can cross the epithelial cell layer of mucous membranes. The organism travels from the site of inoculation down the lymphatic channels to multiply within mononuclear phagocytes of the lymph nodes it passes.

In developed nations, it was considered rare before 2003. However, a recent outbreak in the Netherlands among gay men has led to an increase of LGV in Europe and the United States.

LGV was first described by Wallace in 1833 and again by Durand, Nicolas, and Favre in 1913. Since the 2004 Dutch outbreak many additional cases have been reported, leading to greater surveillance. Soon after the initial Dutch report, national and international health authorities launched warning initiatives and multiple LGV cases were identified in several more European countries (Belgium, France, the UK, Germany, Sweden, Italy and Switzerland) and the US and Canada. All cases reported in Amsterdam and France and a considerable percentage of LGV infections in the UK and Germany were caused by a newly discovered *Chlamydia* variant, L2b, a.k.a. the Amsterdam variant. The L2b variant could be traced back and was isolated from anal swabs of men who have sex with men (MSM) who visited the STI city clinic of San Francisco in 1981. This finding suggests that the recent LGV outbreak among MSM in industrialised countries is a slowly evolving epidemic. The L2b serovar has also been identified in Australia.

### Signs and symptoms

The clinical manifestation of LGV depends on the site of entry of the infectious organism (the sex contact site) and the stage of disease progression.

Inoculation at the mucous lining of external sex organs (penis and vagina) can lead to the inguinal syndrome named after the formation of buboes or abscesses in the groin (inguinal) region where draining lymph nodes are located.

These signs usually appear from 3 days to a month after exposure.

The rectal syndrome (lymphogranuloma venereum proctitis, or LGVP) arises if the infection takes place via the rectal mucosa (through anal sex) and is mainly characterized by proctocolitis or proctitis symptoms. The pharyngeal syndrome is rare. It starts after infection of pharyngeal tissue, and buboes in the neck region can occur.

### Primary stage

LGV may begin as a self-limited painless genital ulcer that occurs at the contact site 3–12 days after infection. Women rarely notice a primary infection because the initial ulceration where the organism penetrates the mucosal layer is often located out of sight, in the vaginal wall. In men fewer than one-third of those infected notice the first signs of LGV. This primary stage heals in a few days. Erythema nodosum occurs in 10% of cases.

### Secondary stage

The secondary stage most often occurs 10–30 days later, but can present up to six months later. The



infection spreads to the lymph nodes through lymphatic drainage pathways. The most frequent presenting clinical manifestation of LGV among males whose primary exposure was genital is unilateral (in two-thirds of cases) lymphadenitis and lymphangitis, often with tender inguinal and/or femoral lymphadenopathy because of the drainage pathway for their likely infected areas. Lymphangitis of the dorsal penis may also occur and resembles a string or cord. If the route was anal sex, the infected person may experience lymphadenitis and lymphangitis noted above. They may instead develop proctitis, inflammation limited to the rectum (the distal 10–12 cm) that may be associated with anorectal pain, tenesmus, and rectal discharge, or proctocolitis, inflammation of the colonic mucosa extending to 12 cm above the anus and associated with symptoms of proctitis plus diarrhea or abdominal cramps.

In addition, symptoms may include inflammatory involvement of the perirectal or perianal lymphatic tissues. In females, cervicitis, perimetritis, or salpingitis may occur as well as lymphangitis and lymphadenitis in deeper nodes. Because of lymphatic drainage pathways, some patients develop an abdominal mass which seldom suppurates, and 20–30% develop inguinal lymphadenopathy. Systemic signs which can appear include fever, decreased appetite, and malaise.

Diagnosis is more difficult in women and men who have sex with men (MSM) who may not have the inguinal symptoms.

Over the course of the disease, lymph nodes enlarge, as may occur in any infection of these areas as well. Enlarged nodes are called buboes. Buboes are commonly painful.

Nodes commonly become inflamed, thinning and fixation of the overlying skin. These changes may progress to necrosis, fluctuant and suppurative lymph nodes, abscesses, fistulas, strictures, and sinus tracts. During the infection and when it subsides and healing takes place, fibrosis may occur.

This can result in varying degrees of lymphatic obstruction, chronic edema, and strictures. These late stages characterised by fibrosis and edema are also known as the third stage of LGV, and are mainly permanent.

Treatment involves antibiotics and may involve drainage of the buboes or abscesses by needle aspiration or incision. Further supportive measure may need to be taken: dilatation of the rectal stricture, repair of rectovaginal fistulae, or colostomy for rectal obstruction.

Common antibiotic treatments include tetracycline (doxycycline) (all tetracyclines, including doxycycline, are contraindicated during pregnancy and in children due to effects on bone development and tooth discoloration), and erythromycin. Azithromycin is also a drug of choice in LGV.



## **Mycoplasma Genitalium (MGEN)**

*Mycoplasma genitalium* (MG, commonly known as Mgen), is a sexually transmitted, small and pathogenic bacterium that lives on the mucous epithelial cells of the urinary and genital tracts in humans. Medical reports published in 2007 and 2015 state Mgen is becoming increasingly common. Resistance to multiple antibiotics is becoming prevalent, including to azithromycin, which until recently was the most reliable treatment. The bacteria was first isolated from the urogenital tract of humans in 1981, and was eventually identified as a new species of *Mycoplasma* in 1983. It can cause negative health effects in men and women. It also increases the risk factor for HIV spread with higher occurrences in those previously treated with the azithromycin antibiotics.

Specifically, it causes urethritis in both men and women, and also cervicitis and pelvic inflammation in women. It presents clinically similar symptoms to that of *Chlamydia trachomatis* infection and has shown higher incidence rates, compared to both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in some populations. Its complete genome sequence was published in 1995 (size 0.58 Mbp, with 475 genes). It was regarded as a cellular unit with the smallest genome size (in Mbp) until 2003 when a new species of Archaea, namely *Nanoarchaeum equitans*, was sequenced (0.49 Mbp, with 540 genes).

However, Mgen still has the smallest genome of any known (naturally occurring) self-replicating organism and thus is often the organism of choice in minimal genome research.

The synthetic genome of Mgen named *Mycoplasma genitalium* JCVI-1.0 (after the research centre, J. Craig Venter Institute, where it was synthesised) was produced in 2008, becoming the first organism with a synthetic genome. In 2014, a protein was described called Protein M from *M. genitalium*.

### Signs and symptoms

Infection with Mgen produces a combination of clinical symptoms, but can be asymptomatic.

It causes inflammation in the urethra (urethritis) both in men and women, which is associated with mucopurulent discharge in the urinary tract, and burning while urinating. In women, it causes cervicitis and pelvic inflammatory diseases (PID), including endometritis and salpingitis.

Women may also experience bleeding after sex and it is also linked with tubal factor infertility.

For men, the most common signs are painful urination or a watery discharge from the penis. Polymerase chain reaction analyses indicated that it is a cause of acute non-gonococcal urethritis (NGU) and probably chronic NGU. It is strongly associated with persistent and recurring nongonococcal urethritis (NGU) responsible for 15 percent to 20 percent of symptomatic NGU cases in men. Unlike other *Mycoplasma*, the infection is not associated with bacterial vaginosis. It is highly associated with the intensity of HIV infection. Some scientists are doing research to see if Mgen could play a role in the development of prostate and ovarian cancers and lymphomas in some individuals. These studies have yet to find conclusive evidence to suggest a link.

The U.S. Centers for Disease Control and Prevention recommends a step-wise treatment approach for *Mycoplasma genitalium* with doxycycline for 7 days followed immediately by a 7 day course of moxifloxacin as the preferred therapy due to high rates of macrolide resistance. If resistance assay testing is available, and the *Mycoplasma genitalium* is sensitive to macrolides; the CDC recommends a 7 day course of doxycycline followed by a 4 day course of azithromycin. If moxifloxacin is not available; the CDC recommends as an alternative regimen, 7 days of doxycycline followed by the 4 day course of azithromycin, with a test of cure 21 days after treatment being required due to the high rate of macrolide resistance. The CDC notes that beta



lactam antibiotic are not effective against mycoplasmagenitalium as the organism lacks a cell wall.

Treatment of *Mycoplasma genitalium* infections is becoming increasingly difficult due to rapidly growing antimicrobial resistance. Diagnosis and treatment is further hampered by the fact that *Mycoplasma genitalium* infections are not routinely tested. Studies have demonstrated that a 5-day course of azithromycin has a superior cure rate compared to a single, larger dose. Further, a single dose of azithromycin can lead to the bacteria becoming resistant to azithromycin.

Among Swedish patients, doxycycline was shown to be relatively ineffective (with a cure rate of 48% for women and 38% for men); and treatment with a single dose of azithromycin is not prescribed due to it inducing antimicrobial resistance. The five-day treatment with azithromycin showed no development of antimicrobial resistance. Based on these findings, UK doctors are moving to the 5-day azithromycin regimen. Doxycycline is also still used, and moxifloxacin is used as a second-line treatment in case doxycycline and azithromycin are not able to eradicate the infection. In patients where doxycycline, azithromycin and moxifloxacin all failed, pristinamycin has been shown to still be able to eradicate the infection.



## **Pediculosis Pubis**

Pediculosis pubis (also known as "crabs" and "pubic lice") is an infestation by the pubic louse, *Phthirus pubis*, a wingless insect which feeds on blood and lays its eggs (nits) on mainly pubic hair. Less commonly, hair near the anus, armpit, beard, eyebrows, moustache, and eyelashes may be involved. It is usually acquired during sex, but can be spread via bedding, clothing and towels, and is more common in crowded conditions where there is close contact between people.

The main symptom is an intense itch in the groin, particularly at night. There may be some grey-blue discoloration at the feeding site, and eggs and lice may be visible. Scratchmarks, crusting and scarring may be seen, and there may be signs of secondary bacterial infection.

Diagnosis is by visualising the nits or live lice, either directly or with a magnifying glass. Investigations for other sexually transmitted infections (STIs) are usually performed.

First line treatment usually contains permethrin and is available over the counter. Two rounds of treatment at least a week apart are usually required to kill newly hatched nymphs. Washing bedding and clothing in hot water kills the lice, and transmission can be prevented by avoiding sexual contact until no signs of infestation exist. Eggs may be removed by combing pubic hair with a comb dipped in vinegar. Sexual partners should be evaluated and treated.

Infestation with pubic lice is found in all parts of the world, occurs in all ethnic groups and all levels of society. Worldwide, the condition affects about 2% of the population.

### Signs and symptoms

The onset of symptoms is typically three weeks after the first infestation of lice and is mainly an intense itch in the pubic area and groin, particularly at night, resulting from an allergic reaction to the saliva of feeding lice. In some infestations, a characteristic grey-blue or slate coloration macule appears (*maculae caeruleae*) at the feeding site, which may last for days. Nits or live lice may be seen crawling on the skin. Louse droppings may be noticed as a black powder in the underwear.

Scratch marks, crusting, scarring, rust-colored faecal material, blood stained underwear and secondary bacterial infection may sometimes be seen. Large lymph nodes in the groin and armpits may be felt. Some people with pubic lice infestation may not have any symptoms.

### Spread

Pubic lice are usually transmitted from one person to another during vaginal, oral or anal sex, whether a condom is used or not. One sexual encounter with an infected person carries a high risk of catching pubic lice.

In some circumstances transmission can occur through kissing and hugging, and less likely via bedding, clothing and towels. The lice spread more easily in crowded conditions where the distance between people is close, allowing the lice to crawl from one person to another.

Infestation in a young child or teenager may indicate sexual abuse.

Pubic lice can be treated at home. Available treatments may vary from country to country and include mainly permethrin-containing creams and lotions applied to cool dry skin.

Treatment with medication is combined with combing pubic hair with a fine-toothed comb after applying



vinegar directly to skin or dipping the comb in vinegar, to remove nits. It is recommended to wash bedding, clothing and towels in hot water or preferably in a washing machine at 50°C or higher. When this is not possible, the clothing can be stored in a sealed plastic bag for at least three days. Re-infestation can be prevented by wearing clean underwear at the start of treatment and after completing treatment. Shaving the affected hairs is not essential.

#### First line

At first, treatment is usually with topical permethrin 1% cream, which can be bought over the counter without a prescription. It is applied to the areas affected by pubic lice and washed off after 10 minutes. Brands of permethrin include 'Lyclear', available in the UK as a cream rinse or dermal cream at 5% strengths. In the US, permethrin may be familiar as NIX, Actin and Elimite.

An alternative is the combination of pyrethrins and piperonyl butoxide, in a topical application, which include the brands Licide, and A-200, Pronto and RID shampoos. These medications are safe and effective when used exactly according to the instructions in the package or on the label. To kill newly hatched lice, both treatments can be repeated within the following seven to ten days.

European guidelines state alternatives to permethrin as including either the application of 0.2% phenothrin (washed off after two hours), or 0.5% malathion lotions (washed off after 12 hours). The CDC states alternatives as topical 0.5% malathion or oral ivermectin.

#### Other treatments

Lindane is still used in a shampoo form in some non-European countries. Its licence was withdrawn by the European Medicines Agency in 2008. It may be considered as a last resort in some people who show resistance to other treatments, but is not recommended to be used for a second round of treatment. Lindane is not recommended in pregnant and breastfeeding women, children under the age of two years, and people who have extensive dermatitis. The FDA warns against use in people with a history of uncontrolled seizure disorders and cautious use in infants, children, the elderly, and individuals with other skin conditions (e.g., atopic dermatitis, psoriasis) and in those who weigh less than 110 lbs (50 kg).

Carbaryl has been used since 1976 but found to have the potential to cause cancer in rodents and not to be as effective as previously thought. It is either not used at all or its use is restricted.

Sexual partners should be evaluated and treated, and sexual contact should be avoided until all partners are better. Because of the strong association between the presence of pubic lice and sexually transmitted infections (STIs), affected people require investigation for other STIs.

#### Eyes

Infestation of the eyes is treated differently to other parts of the body. Lice can be removed with forceps or by removing or trimming the lashes. Eyelashes may be treated with a gentle petroleum jelly for occlusion.



## Scabies

Scabies (also known as the seven-year itch) is a contagious skin infestation by the mite *Sarcoptes scabiei*. The most common symptoms are severe itchiness and a pimple-like rash. Occasionally, tiny burrows may appear on the skin. In a first-ever infection, the infected person will usually develop symptoms within two to six weeks. During a second infection, symptoms may begin within 24 hours. These symptoms can be present across most of the body or just certain areas such as the wrists, between fingers, or along the waistline. The head may be affected, but this is typically only in young children. The itch is often worse at night. Scratching may cause skin breakdown and an additional bacterial infection in the skin.

Scabies is caused by infection with the female mite *Sarcoptes scabiei* var. *hominis*, an ectoparasite. The mites burrow into the skin to live and deposit eggs. The symptoms of scabies are due to an allergic reaction to the mites. Often, only between 10 and 15 mites are involved in an infection. Scabies is most often spread during a relatively long period of direct skin contact with an infected person (at least 10 minutes) such as that which may occur during sex or living together. Spread of the disease may occur even if the person has not developed symptoms yet. Crowded living conditions, such as those found in child-care facilities, group homes, and prisons, increase the risk of spread. Areas with a lack of access to water also have higher rates of disease. Crusted scabies is a more severe form of the disease. It typically only occurs in those with a poor immune system and people may have millions of mites, making them much more contagious. In these cases, spread of infection may occur during brief contact or by contaminated objects. The mite is very small and usually not directly visible. Diagnosis is based on the signs and symptoms.

A number of medications are available to treat those infected, such as ivermectin or permethrin, crotamiton, and lindane creams. Sexual contacts within the last month and people who live in the same house should also be treated at the same time. Bedding and clothing used in the last three days should be washed in hot water and dried in a hot dryer. As the mite does not live for more than three days away from human skin, more washing is not needed. Symptoms may continue for two to four weeks following treatment. If after this time symptoms continue, retreatment may be needed.

Scabies is one of the three most common skin disorders in children, along with ringworm and bacterial skin infections. As of 2015, it affects about 204 million people (2.8% of the world population). It is equally common in both sexes. The young and the old are more commonly affected. It also occurs more commonly in the developing world and tropical climates. The word scabies is from Latin: *scabere*, 'to scratch'. Other animals do not spread human scabies. Infection in other animals is typically caused by slightly different but related mites and is known as sarcoptic mange.

### Signs and symptoms

The characteristic symptoms of a scabies infection include intense itching and superficial burrows. Because the host develops the symptoms as a reaction to the mites' presence over time, typically a delay of four to six weeks occurs between the onset of infestation and the onset of itching. Similarly, symptoms often persist for one to several weeks after successful eradication of the mites. As noted, those re-exposed to scabies after successful treatment may exhibit symptoms of the new infestation in a much shorter period—as little as one to four days.

### Itching



In the classic scenario, the itch is made worse by warmth, and is usually experienced as being worse at night, possibly because distractions are fewer. As a symptom, it is less common in the elderly.

#### Rash

The superficial burrows of scabies usually occur in the area of the finger webs, feet, ventral wrists, elbows, back, buttocks, and external genitals. Except in infants and the immunosuppressed, infection generally does not occur in the skin of the face or scalp. The burrows are created by excavation of the adult mite in the epidermis. Acropustulosis, or blisters and pustules on the palms and soles of the feet, are characteristic symptoms of scabies in infants.

In most people, the trails of the burrowing mites are linear or S-shaped tracks in the skin often accompanied by rows of small, pimple-like mosquito or insect bites. These signs are often found in crevices of the body, such as on the webs of fingers and toes, around the genital area, in stomach folds of the skin, and under the breasts of women.

Symptoms typically appear two to six weeks after infestation for individuals never before exposed to scabies. For those having been previously exposed, the symptoms can appear within several days after infestation. However, symptoms may appear after several months or years.

#### Crusted scabies

The elderly, disabled, and people with impaired immune systems, such as those with HIV/AIDS, cancer, or those on immunosuppressive medications, are susceptible to crusted scabies (also called Norwegian scabies). On those with weaker immune systems, the host becomes a more fertile breeding ground for the mites, which spread over the host's body, except the face.

The mites in crusted scabies are not more virulent than in noncrusted scabies; however, they are much more numerous (up to two million). People with crusted scabies exhibit scaly rashes, slight itching, and thick crusts of skin that contain large numbers of scabies mites. For this reason, persons with crusted scabies are more contagious to others than those with typical scabies. Such areas make eradication of mites particularly difficult, as the crusts

protect the mites from topical miticides/scabicides, necessitating prolonged treatment of these areas.

Mass-treatment programs that use topical permethrin or oral ivermectin have been effective in reducing the prevalence of scabies in a number of populations. No vaccine is available for scabies. The simultaneous treatment of all close contacts is recommended, even if they show no symptoms of infection (asymptomatic), to reduce rates of recurrence. Since mites can survive for only two to three days without a host, other objects in the environment pose little risk of transmission except in the case of crusted scabies. Therefore, cleaning is of little importance. Rooms used by those with crusted scabies require thorough cleaning.

A number of medications are effective in treating scabies. Treatment should involve the entire household, and any others who have had recent, prolonged contact with the infested individual.

Options to control itchiness include antihistamines and prescription anti-inflammatory agents.

Bedding, clothing and towels used during the previous three days should be washed in hot water and dried in a hot dryer.

#### Permethrin

Permethrin, a pyrethroid insecticide, is the most effective treatment for scabies, and remains the treatment of choice. It is applied from the neck down, usually before sleep, and left on for about eight to 14 hours, then washed off in the morning. Care should be taken to coat the entire skin surface, not just symptomatic areas; any patch of skin left untreated can provide a "safe haven" for one or more mites to survive. One application is normally sufficient, as permethrin kills eggs and hatchlings, as well as adult mites, though many physicians recommend a second application three to seven days later as a precaution.



Crusted scabies may require multiple applications, or supplemental treatment with oral ivermectin. Permethrin may cause slight irritation of the skin that is usually tolerable.

#### Ivermectin

Oral ivermectin is effective in eradicating scabies, often in a single dose. It is the treatment of choice for crusted scabies, and is sometimes prescribed in combination with a topical agent. It has not been tested on infants, and is not recommended for children under six years of age.

Topical ivermectin preparations have been shown to be effective for scabies in adults, though only one such formulation is available in the United States at present, and it is not FDA-approved as a scabies treatment. It has also been useful for sarcoptic mange (the veterinary analog of human scabies).

One review found that the efficacy of permethrin is similar to that of systemic or topical ivermectin. A separate review found that although oral ivermectin is usually effective for treatment of scabies, it does have a higher treatment failure rate than topical permethrin. Another review found that oral ivermectin provided a reasonable balance between efficacy and safety. A study has demonstrated that scabies is markedly reduced in populations

taking ivermectin regularly; the drug is widely used for treating scabies and other parasitic diseases particularly among the poor and disadvantaged in the tropics, beginning with the developer Merck providing the drug at no cost to treat onchocerciasis from 1987.

#### Others

Other treatments include lindane, benzyl benzoate, crotamiton, malathion, and sulfur preparations. Lindane is effective, but concerns over potential neurotoxicity have limited its availability in many countries. It is banned in California, but may be used in other states as a second-line treatment. Sulfur ointments or benzyl benzoate are often used in the developing world due to their low cost; Some 10% sulfur solutions have been shown to be effective, and sulfur ointments are typically used for at least a week, though many people find the odor of sulfur products unpleasant. Crotamiton has been found to be less effective than permethrin in limited studies. Crotamiton or sulfur preparations are sometimes recommended instead of permethrin for children, due to concerns over dermal absorption of permethrin.



### **Nongonoccal Urethritis(NGU)**

Nongonococcal urethritis (NGU) is an inflammation of the urethra that is not caused by gonorrheal infection.

For treatment purposes, doctors usually classify infectious urethritis in two categories: gonococcal urethritis, caused by gonorrhea, and nongonococcal urethritis (NGU).

The symptoms of urethritis can include pain or a burning sensation upon urination (dysuria), a white/cloudy discharge and a feeling that one needs to pass urine frequently. For men, the signs and symptoms are discharge from the penis, burning or pain when urinating, itching, irritation, or tenderness. In women, the signs and symptoms are discharge from vagina, burning or pain when urinating, anal or oral infections, abdominal pain, or abnormal vaginal bleeding, which may be an indication that the infection has progressed to Pelvic Inflammatory Disease.

NGU is transmitted by touching the mouth, penis, vagina or anus by penis, vagina or anus of a person who has NGU.

NGU is more common in men than women. Men may have a discharge (strange liquid) from the penis, pain when urinating, and itching, irritation or tenderness around the opening of the penis. Women might not have any symptoms and may not know they have NGU until severe problems occur. Women might have discharge from the vagina, burning or pain when urinating, pain in the abdominal (stomach) area, or bleeding from the vagina that is not from a monthly period.

(This may be a sign that NGU has become worse and turned into Pelvic Inflammatory Disease, or PID).

Treatment is based on the prescription and use of the proper antibiotics depending on the strain of the ureaplasma.

Because of its multi-causative nature, initial treatment strategies involve using a broad range antibiotic that is effective against chlamydia (such as doxycycline). It is imperative that both the patient and any sexual contacts be treated. Women infected with the organisms that cause NGU may develop pelvic inflammatory disease. If symptoms persist, follow-up with a urologist may be necessary to identify the cause.

According to a study, tinidazole used with doxycycline or azithromycin may cure NGU better than when doxycycline or azithromycin is used alone.

If left untreated, complications include epididymitis and infertility. Consistent and correct use of latex condoms during sexual activity greatly reduces the likelihood of infection.



## Epididymitis

Epididymitis is a medical condition characterized by inflammation of the epididymis, a curved structure at the back of the testicle. Onset of pain is typically over a day or two. The pain may improve with raising the testicle. Other symptoms may include swelling of the testicle, burning with urination, or frequent urination. Inflammation of the testicle is commonly also present.

In those who are young and sexually active gonorrhoea and chlamydia are frequently the underlying cause. In older males and men who practice insertive anal sex, enteric bacteria are a common cause. Diagnosis is typically based on symptoms. Conditions that may result in similar symptoms include testicular torsion, inguinal hernia, and testicular cancer.

Ultrasound can be useful if the diagnosis is unclear.

Treatment may include pain medications, NSAIDs, and elevation. Recommended antibiotics in those who are young and sexually active are ceftriaxone and doxycycline. Among those who are older, ofloxacin may be used. Complications include infertility and chronic pain. People aged 15 to 35 are most commonly affected, with about 600,000 people within this age group affected per year in the United States.

### Signs and symptoms

Those aged 15 to 35 are most commonly affected. The acute form usually develops over the course of several days, with pain and swelling frequently in only one testis, which will hang low in the scrotum. There will often be a recent history of dysuria or urethral discharge. Fever is also a common symptom. In the chronic version, the patient may have painful point tenderness but may or may not have an irregular epididymis upon palpation, though palpation may reveal an indurated epididymis. A scrotal ultrasound may reveal problems with the epididymis, but such an ultrasound may also show nothing unusual. The majority of patients who present with chronic epididymitis have had symptoms for over five years.

In both the acute and chronic forms, antibiotics are used if an infection is suspected. The treatment of choice is often azithromycin and cefixime to cover both gonorrhoeae and chlamydia.

Fluoroquinolones are no longer recommended due to widespread resistance of gonorrhoeae to this class. Doxycycline may be used as an alternative to azithromycin. In chronic epididymitis, a four- to six-week course of antibiotics may be prescribed to ensure the complete eradication of any possible bacterial cause, especially the various chlamydiae.

For cases caused by enteric organisms (such as *E. coli*), ofloxacin or levofloxacin are recommended.

In children, fluoroquinolones and doxycycline are best avoided. Since bacteria that cause urinary tract infections are often the cause of epididymitis in children, co-trimoxazole or suited penicillins (for example, cephalexin) can be used.

Household remedies such as elevation of the scrotum and cold compresses applied regularly to the scrotum may relieve the pain in acute cases. Painkillers or anti-inflammatory drugs are often used for treatment of both chronic and acute forms. Hospitalisation is indicated for severe cases, and check-ups can ensure the infection has cleared up. Surgical removal of the epididymis is rarely necessary, causes sterility, and only gives relief from pain in approximately 50% of cases. However, in acute suppurating epididymitis (acute epididymitis with a



discharge of pus), an epididymotomy may be recommended; in refractory cases, a full epididymectomy may be required. In cases with unrelenting testicular pain, removal of the entire testicle—orchietomy— may also be warranted.

It is generally believed that most cases of chronic epididymitis will eventually "burn out" of patient's system if left untreated, though this might take years or even decades. However, some prostate-related medications have proven effective in treating chronic epididymitis, including doxazosin.

### **Cervicitis**

Cervicitis is inflammation of the uterine cervix. Cervicitis in women has many features uncommon with urethritis in men and many cases are caused by sexually transmitted infections.

Non-infectious causes of cervicitis can include intrauterine devices, contraceptive diaphragms, and allergic reactions to spermicides or latex condoms. Cervicitis affects over half of all women during their adult life.

#### **Symptoms and signs**

Cervicitis may have no symptoms. If symptoms do manifest, they may include: Abnormal vaginal bleeding after intercourse between periods.

Unusual gray, white, or yellow vaginal discharge. Painful sexual intercourse.

Pain in the vagina.

Pressure or heaviness in the pelvis. Frequent, painful urination

The risk of contracting cervicitis from STIs can be reduced by using condoms during every sexual encounter. Condoms are effective against the spread of STIs like chlamydia and gonorrhea that cause cervicitis. Also, being in a long-term monogamous relationship with an uninfected partner can lower the risk of an STI.

Ensuring that foreign objects like tampons are properly placed in the vagina and following instructions how long to leave it inside, how often to change it, and/or how often to clean it can reduce the risk of cervicitis. In addition, avoiding potential irritants like douches and deodorant tampons can prevent cervicitis.

Non-infectious causes of cervicitis are primarily treated by eliminating or limiting exposure to the irritant. Antibiotics, usually azithromycin or doxycycline, or antiviral medications are used to treat infectious causes.

Women at increased risk of sexually transmitted infections (i.e., less than 25 years of age and a new sexual partner, a sexual partner with other partners, or a sexual partner with a known sexually transmitted infection), should be treated presumptively for chlamydia and possibly gonorrhea, particularly if follow-up care cannot be ensured or diagnostic testing is not possible. For lower risk women, deferring treatment until test results are available is an option.

To reduce the risk of reinfection, women should abstain from sexual intercourse for seven days after treatment is started. Also, sexual partners (within the last sixty days) of anyone with infectious cervicitis should be referred for evaluation or treated through expedited partner therapy (EPT). EPT is the process by which a clinician treats the sexual partner of a patient diagnosed with a sexually transmitted infection without first meeting or examining the partner. Sexual partners should also avoid sexual intercourse until they and their partners are adequately treated.



Untreated cervicitis is also associated with an increased susceptibility to HIV infection. Women with infectious cervicitis should be tested for other sexually transmitted infections, including HIV and syphilis.

Cervicitis should be followed up. Women with a specific diagnosis of chlamydia, gonorrhea, or trichomonas should see a clinician in three months after treatment for repeat testing because they are at higher risk of getting reinfected, regardless of whether their sex partners were treated.

Treatment in pregnant women is the same as those who are not pregnant.

### **Proctitis**

Proctitis is an inflammation of the anus and the lining of the rectum, affecting only the last 6 inches of the rectum.

A common symptom is a continual urge to have a bowel movement—the rectum could feel full or have constipation. Another is tenderness and mild irritation in the rectum and anal region.

A serious symptom is pus and blood in the discharge, accompanied by cramps and pain during the bowel movement. If there is severe bleeding, anemia can result, showing symptoms such as pale skin, irritability, weakness, dizziness, brittle nails, and shortness of breath.

Symptoms are ineffectual straining to empty the bowels, diarrhea, rectal bleeding and possible discharge, a feeling of not having adequately emptied the bowels, involuntary spasms and cramping during bowel movements, left-sided abdominal pain, passage of mucus through the rectum, and anorectal pain.

Sexually transmitted proctitis Gonorrhea

(Gonococcal proctitis)

This is the most common cause. Strongly associated with anal intercourse. Symptoms include soreness, itching, bloody or pus-like discharge, or diarrhea. Other rectal problems that may be present are anal warts, anal tears, fistulas, and hemorrhoids.

Chlamydia (chlamydia proctitis)

Accounts for twenty percent of cases. People may show no symptoms, mild symptoms, or severe symptoms. Mild symptoms include rectal pain with bowel movements, rectal discharge, and cramping. With severe cases, people may have discharge containing blood or pus, severe rectal pain, and diarrhea. Some people have rectal strictures, a narrowing of the rectal passageway. The narrowing of the passageway may cause constipation, straining, and thin stools.

Herpes Simplex Virus 1 and 2 (herpes proctitis)

Symptoms may include multiple vesicles that rupture to form ulcers, tenesmus, rectal pain, discharge, hematochezia. The disease may run its natural course of exacerbations and remissions but is usually more prolonged and severe in patients with immunodeficiency disorders. Presentations may resemble dermatitis or decubitus ulcers in debilitated, bedridden patients. A secondary bacterial infection may be present.

Syphilis (syphilitic proctitis)

The symptoms are similar to other causes of infectious proctitis; rectal pain, discharge, and spasms during bowel movements, but some people may have no symptoms. Syphilis occurs in three stages.

The primary stage: One painless sore, less than an inch across, with raised borders found at the site of sexual contact, and during acute stages of infection, the lymph nodes in the groin become diseased, firm, and rubbery.

The secondary stage: A contagious diffuse rash that may appear over the entire body, particularly on the hands and feet.

The third stage: Occurs late in the course of syphilis and affects mostly the heart and nervous system.



Treatment for proctitis varies depending on severity and the cause. For example, the physician may prescribe antibiotics for proctitis caused by bacterial infection. If the proctitis is caused by Crohn's disease or ulcerative colitis, the physician may prescribe the drug 5-aminosalicylic acid (5ASA) or corticosteroids applied directly to the area in enema or suppository form, or taken orally in pill form. Enema and suppository applications are usually more effective, but some patients may require a combination of oral and rectal applications.

Another treatment available is that of fiber supplements such as Metamucil. Taken daily these may restore regularity and reduce pain associated with proctitis.

Chronic radiation proctitis is usually treated first-line with sucralfate enemas. These are noninvasive and are effective in diffuse, distal disease. Other treatments may include mesalamine suppositories, vitamin E, hyperbaric oxygen, or short chain fatty acid enemas; however these treatments are only supported by observational or anecdotal evidence.



## Urethritis

Urethritis is the inflammation of the urethra. The most common symptoms include painful or difficult urination and urethral discharge. It is a commonly treatable condition usually caused by infection with bacteria. This bacterial infection is often sexually transmitted, but not in every instance; it can be idiopathic, for example. Some incidence of urethritis can appear asymptomatic as well.

Symptoms vary based on the cause of the diseases. For infectious causes of urethritis, symptoms may start a few weeks to several months after infection. Non-infectious causes of urethritis commonly show symptoms after a few days. Common symptoms include painful urination, continuous urge to urinate, itching and, urethral discharge. Additional symptoms vary based on gender. Men may experience blood in the urine or semen, itching, tenderness, or swelling of the penis, enlarged lymph nodes in the groin area, and/or pain with intercourse or ejaculation. Women may experience abdominal pain, pelvic pain, pain with intercourse, or vaginal discharge. Nongonococcal urethritis typically does not have noticeable symptoms in women, however, the infection can spread to parts of the female reproductive system.

Primary prevention can be accomplished by the reduction of modifiable risk factors that increase the likelihood of developing urethritis. These factors include, but are not limited to, sexual intercourse (particularly unprotected intercourse) and genital irritation from contact with tight clothing, physical activity, and various irritants such as soap, lotion and spermicides.

Bacterial infections leading to gonococcal and non-gonococcal urethritis can be prevented by:

Sexual abstinence.

Use of barrier contraception, such as condoms.

Pre-exposure vaccination: HPV and Hepatitis B vaccines. Reducing number of sexual partners.

Chlorhexidine is an antibacterial agent that covers a wide spectrum of gram-positive and gram-negative bacteria. Rinsing with 15 ml of a 0.12% or 10 ml of 0.2% chlorhexidine solution for 30 seconds produced large and prolonged reductions in salivary bacterial counts within 7 hours of its use. One hypothesis in 2010 posed the potential use of chlorhexidine rinsing before oral sex as a prevention strategy of recurrent non-gonococcal urethritis caused by bacteria entering the urethra from oral cavity following "insertive oral intercourse", particularly in men. However, actual clinical studies are yet to be carried out in order to prove this hypothesis. Antimicrobials are generally the drug of choice for gonococcal and non-gonococcal infections. The CDC in 2015 suggests using a dual therapy that consists of two antimicrobials that have different mechanisms of action would be an effective treatment strategy for urethritis and it could also potentially slow down antibiotic resistance.

A variety of drugs may be prescribed based on the cause of urethritis:

Gonococcal urethritis (caused by *N. gonorrhoeae*): The CDC recommends administering an injection dose of



ceftriaxone 250 mg intramuscularly and oral dose of azithromycin 1g simultaneously. Cefixime 400 mg oral single dose can be used as an alternative if ceftriaxone is not available.

Non-gonococcal urethritis (caused by *Chlamydia trachomatis*): The CDC recommends administering an oral single dose of azithromycin 1g or a 7-day course of doxycycline 100mg orally twice daily.

Alternative treatments can also be used when the above options are not available: Erythromycin base 500 mg orally four times daily for 7 days.

Erythromycin ethylsuccinate 800 mg orally four times daily for 7 days. Levofloxacin 500 mg orally once daily for 7 days.

Ofloxacin 300 mg orally twice daily for 7 days.

Treatment for both gonococcal and non-gonococcal urethritis is suggested to be given under direct observation in a clinic or healthcare facility in order to maximize compliance and effectiveness.

For non-medication management, proper perineal hygiene should be stressed. This includes avoiding use of vaginal deodorant sprays and proper wiping after urination and bowel movements. Sexual intercourse should be avoided at least 7 days after completion of treatment (and until symptoms resolves, if present). Past and current sexual partners should also be assessed and treated.

Individuals displaying persistence or recurrence of symptoms should be instructed for possible re-evaluation. Although there is no standard definition, persistent urethritis is defined as urethritis that has failed to display improvement within the first week of initial therapy. Additionally, recurrent urethritis is defined as urethritis reappearing within 6 weeks after a previous episode of non-gonococcal urethritis. If recurrent symptoms are supported by microscopic evidence of urethritis, then re-treatment is appropriate. The following treatment recommendations are limited and based on clinical experience, expert opinions and guidelines for recurrent or persistent nongonococcal urethritis:

If doxycycline was prescribed as initial therapy, give azithromycin 500 mg or 1 gram for the first day, then give azithromycin 250 mg once daily for 4 days plus metronidazole 400 – 500mg twice daily for 5 days.

If azithromycin was prescribed as initial therapy, then give doxycycline 100 mg twice daily for 7 days plus metronidazole 400 – 500 mg twice daily for 5 – 7 days.

Moxifloxacin 400 mg orally once daily for 7 – 14 days can be given with use of caution, if macrolide-resistant *M. genitalium* infection is demonstrated.

Appropriate treatment for these individuals may require further referral to a urologist if symptoms persist after initial treatment.



## Vaginitis

Vaginitis, also known as vulvovaginitis, is inflammation of the vagina and vulva. Symptoms may include itching, burning, pain, discharge, and a bad smell. Certain types of vaginitis may result in complications during pregnancy.

The three main causes are infections, specifically bacterial vaginosis, vaginal yeast infection, and trichomoniasis. Other causes include allergies to substances such as spermicides or soaps or as a result of low estrogen levels during breast-feeding or after menopause. More than one cause may exist at a time. The common causes vary by age. Prepubescent girls are often at risk for development of vulvovaginitis because of low amounts of estrogen and an underdeveloped labia minora.

Diagnosis generally include examination, measuring the pH, and culturing the discharge. Other causes of symptoms such as inflammation of the cervix, pelvic inflammatory disease, cancer, foreign bodies, and skin conditions should be ruled out.

Treatment depends on the underlying cause. Infections should be treated. Sitz baths may help with symptoms. Soaps and feminine hygiene products such as sprays should not be used. About a third of women have vaginitis at some point in time. Women of reproductive age are most often affected.

### Signs and symptoms

A woman may have vaginal irritation, itching, or burning or may notice a foul-smelling or abnormal discharge that could appear green or yellow.

The following signs or symptoms may indicate the presence of infection: Irritation or itching of the genital area.

Inflammation (irritation, redness, and swelling caused by the presence of extra immune cells) of the labia majora, labia minora, or perineal area.

Vaginal discharge.

Foul vaginal odor.

Pain/irritation with sexual intercourse.

### Complications

Vaginal infections left untreated can lead to further complications, especially for the pregnant woman. For bacterial vaginosis, these include "premature delivery, postpartum infections, clinically apparent and subclinical pelvic inflammatory disease, [as well as] postsurgical complications (after abortion, hysterectomy, caesarian section), increased vulnerability to HIV infection and, possibly, infertility". Studies have also linked trichomoniasis with increased likelihood of acquiring HIV; theories include that "vaginitis increases the number of immune cells at the site of infection, and HIV then



infects those immune cells." Other theories suggest that trichomoniasis increases the amount of HIV genital shedding, thereby increasing the risk of transmission to sexual partners. While the exact association between trichomoniasis infection and HIV genital shedding has not been consistently demonstrated, "there is good evidence that TV treatment reduces HIV genital shedding. Five studies were reported in the literature and, of these, four found a decrease in HIV genital shedding after TV treatment."

Further, there are complications which lead to daily discomfort such as: Persistent discomfort.

Superficial skin infection (from scratching).

Complications of the causative condition (such as gonorrhea and candida infection).

The cause of the infection determines the appropriate treatment. It may include oral or topical antibiotics and/or antifungal creams, antibacterial creams, or similar medications. A cream containing cortisone may also be used to relieve some of the irritation. If an allergic reaction is involved, an antihistamine may also be prescribed. For women who have irritation and inflammation caused by low levels of estrogen (postmenopausal), a topical estrogen cream might be prescribed.

The following are typical treatments for trichomoniasis, bacterial vaginosis, and yeast infections:

**Trichomoniasis:** Oral treatment with either metronidazole or tinidazole. "Sexual partner(s) should be treated simultaneously. Patients should be advised to avoid sexual intercourse for at least 1 week and until they and their partner(s) have completed treatment and follow-up."

**Bacterial vaginosis:** The most commonly used antibiotics are metronidazole, available in both pill and gel form, and clindamycin available in both pill and cream form.

**Yeast infections:** Local azole, in the form of ovula and cream. All agents appear to be equally effective. These anti-fungal medications, which are available in over the counter form, are generally used to treat yeast infections. Treatment may last anywhere between one, three, or seven days.