Sexually Transmitted Diseases

Overview

Background

Sexually transmitted diseases (STDs) incorporate a variety of clinical syndromes caused by pathogens that may be acquired and transmitted through sexual activity. Among persons with HIV (or at high risk for acquiring HIV), the diagnosis and management of STDs is important for three main reasons: (1) STDs are common in persons with HIV, (2) HIV can potentially impact the severity and response to treatment of STDs, and (3) development of STDs can impact the transmission of HIV. Despite education and prevention efforts, national trends indicate a rising incidence of several STDs, especially among men with HIV who have sex with men. Clinicians providing care to persons with HIV play a crucial role in STD prevention through regular risk assessment and counseling, vaccination for vaccine-preventable STDs, routine screening, diagnosis and treatment of STDs, and partner services. This Topic Review will explore screening, diagnosis, and treatment strategies for the most common and important STDs that occur among persons with HIV; the recommendations herein are based primarily on the 2015 CDC STD Treatment Guidelines.

Screening for STDs in Persons Living with HIV

In order to adequately address the ongoing burden of sexually transmitted infections in persons with HIV, it is critical to implement routine screening strategies and follow evidence-based treatment guidelines (in coordination with state and local health departments). Toward this end, the 2015 CDC STD Treatment Guidelines outline appropriate STD screening for persons with HIV (Table 1). The highest priority for screening is to test for common curable STDs, including chlamydia, gonorrhea, and syphilis, in men and women, as well as trichomoniasis in women. In sexually active persons with HIV, screening for these STDs should be performed at the initial evaluation and then at least annually thereafter. More frequent screening may be appropriate depending on individual risk behaviors (e.g. history of STDs, exchanging sex for money or drugs, engaging in sex with a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection) and local epidemiology of specific STDs.
**Gonorrhea**

**Introduction**

Gonorrhea is the second most common bacterial sexually transmitted infection, with 583,405 cases reported in the United States in 2018.[7] Gonorrhea is most often diagnosed in younger adults, especially those 20 to 29 years of age (Figure 1).[7] The causative agent is *Neisseria gonorrhoeae*, a gram-negative intracellular diplococcus. Treatment of gonorrhea has been complicated by resistance among *N. gonorrhoeae* isolates to fluoroquinolones, azithromycin, and some cephalosporins. The increases in drug resistance observed with *N. gonorrhoeae* have reached the point where this problem now poses a significant public health threat. Surveillance by clinicians, as well as by state and local health authorities, is critical to determine local resistance patterns and thereby guide treatment recommendations.[8,9]

**Clinical Manifestations**

Similar to *C. trachomatis*, *N. gonorrhoeae* can cause a wide range of clinical manifestations, including urethritis, cervicitis, pelvic inflammatory disease, epididymitis, proctitis, prostatitis, pharyngitis, and neonatal infection. In addition, disseminated gonococcal infection can cause petechial skin rash, septic arthritis, tenosynovitis, and occasionally peritonitis, endocarditis, and meningitis. Urethral infection is typically symptomatic, but pharyngeal and anorectal infection with *N. gonorrhoeae* often occurs without causing symptoms.

**Screening Recommendations**

Available data suggest that inflammatory sexually transmitted infections enhance transmission of HIV,[10,11] so routine screening and treatment of gonorrhea may indirectly reduce the risk of HIV transmission to sexual partners. The 2015 CDC STD Treatment Guidelines recommend the following for gonorrhea screening in persons with HIV:[8]

- Screen all men and women for urogenital gonorrhea infection at baseline and at least annually thereafter, with the frequency depending on the presence of ongoing risk factors and the prevalence of sexually transmitted diseases in the community.
- Screen all men who have sex with men for urethral gonorrhea as well as for rectal and pharyngeal gonorrhea at least annually if they report receptive sex at these sites, regardless of condom use.
- Retesting in 3 months is indicated for men and women found to be positive on initial screening because of high reinfection rates.

**Laboratory Diagnosis**

In the 2014 CDC recommendations for laboratory-based diagnosis of *Neisseria gonorrhoeae*, nucleic acid amplification tests (NAATs) are the preferred diagnostic method, primarily due to superior sensitivity for the detection of *N. gonorrhoeae* at both genital and nongenital sites when compared with culture.[12] There are multiple NAATs that have FDA clearance for diagnostic testing of gonorrhea and chlamydia in genital samples, including for endocervical swabs, vaginal swabs, urethral swabs, and urine.[12] As of May 23, 2019, the FDA has also cleared two NAATs for diagnostic testing of gonorrhea and chlamydia at extragenital sites (pharynx and rectum); the two tests are the Aptima Combo 2 Assay and the Xpert CT/NG.[13]

- **Testing for Gonorrhea in Women**: The recommended sample type for detecting *N. gonorrhoeae* urogenital infections in women is a self- or clinician-collected vaginal swab; self-collected vaginal swab specimens perform at least as well as other approved specimens using NAATs.[12,14,15] Alternatively, an endocervical sample is acceptable if a pelvic examination is indicated. Collecting a first-catch urine sample is also an option for screening in women, but this strategy may detect 10% fewer cases of *N. gonorrhoeae* infection compared with vaginal or endocervical swabs.[12] Use of
Gram’s stain is not recommended for making a diagnosis of gonorrhea on an endocervical or pharyngeal swab sample.[8] Routine screening of extragenital sites (rectum or pharynx) is not recommended in women at this time.[8]

- **Testing for Gonorrhea in Men:** For men, the recommended sample type for detecting *N. gonorrhoeae* urethral infection is a first-catch urine NAAT.[12] The sensitivity of NAAT is superior to culture, and NAAT is the preferred testing method as long as laboratories comply with Clinical Laboratory Improvement Amendments (CLIA) regulations.[12] Of note, a Gram’s stain of a urethral specimen demonstrating the presence of leukocytes with intracellular gram-negative diplococci is highly specific for *N. gonorrhoeae* urethral infection, but due to lower sensitivity should not be used to rule out *N. gonorrhoeae* infection.[1,8] In addition, performing Gram’s stain is not recommended for pharyngeal or rectal specimens.

### Treatment

According to the 2015 CDC STD Treatment Guidelines, the treatment of individuals with urogenital gonorrheal infections is the same for persons with or without HIV.[8] On December 18, 2020, the CDC issued a major update for the treatment of gonococcal infections and these 2020 treatment recommendations are summarized below.[16]

- **Treatment of Uncomplicated Gonococcal Infection of Cervix, Urethra, or Rectum:** For uncomplicated gonococcal infections of the cervix, urethra, or rectum, the recommended regimen is ceftriaxone 500 mg given as a single intramuscular dose, with or without oral doxycycline 100 mg twice daily for 7 days, depending on whether chlamydia infection has been ruled out (Table 2).[16] For pregnant persons azithromycin 1 g as a single oral dose is recommended to treat chlamydia instead of doxycycline. If ceftriaxone is not available, the two options are (1) gentamicin 240 mg given as a single intramuscular dose plus oral azithromycin 2 grams or (2) oral cefixime 800 mg as a single dose.[16] If chlamydia has not been ruled out then doxycycline 100 mg twice daily for 7 days should be added to both of these alternative options.[17]

- **Treatment of Uncomplicated Gonococcal Infection of the Pharynx:** For uncomplicated gonococcal infections of the pharynx, the same treatment regimen is recommended as for treatment for infection of the cervix, urethra, or rectum, except that alternative regimens are not an option and a test-of-cure (using either culture or NAAT) should be performed 10 to 14 days after treatment, regardless of the treatment regimen (Table 3).[16]

- **Patients with Penicillin Allergy:** For individuals with a history of a severe penicillin allergy, the best option is dual therapy with gentamicin 240 mg as a single intramuscular dose plus azithromycin 2 g orally as a single dose, but note that a large randomized clinical trial demonstrated gentamicin is significantly less effective than ceftriaxone plus azithromycin for curing rectal and pharyngeal gonococcal infections.[18]

- **Management of Sex Partners:** All recent sex partners of persons diagnosed with gonorrhea should be referred for evaluation, testing, and presumptive treatment of both gonorrhea and chlamydia. In this context, recent is defined as sex contact within the 60 days preceding onset of symptoms or gonorrhea diagnosis. In the United States, expedited partner therapy may be considered for (1) men who have sex with women only or (2) women who have sex with men only in states where this is allowed by law; individuals diagnosed with gonococcal infection can deliver cefixime 800 mg; if concurrent chlamydia was not excluded in the source individual who was diagnosed with gonorrhea, then the expedited partner therapy should include oral doxycycline 100 mg for 7 days (for nonpregnant persons).[16] The antimicrobial medication must be accompanied by written materials about possible exposure to gonorrhea, the importance of therapy, potential adverse effects of the medications, and the need to seek care for potential complications, including pelvic inflammatory disease. Expedited partner therapy is not recommended for partners of men who have sex with men due to high risk for coexisting STDs or HIV and lack of data in this population.[8]
Chlamydia

Introduction

Chlamydia infections, caused by the intracellular bacteria *Chlamydia trachomatis*, are the most commonly reported STD in the United States, with 1,758,668 reported cases in 2018.[19] Among the reported cases, 66% were females; the highest rates are in females under the age of 25 years, particularly females 20 to 24 years of age (Figure 2).[19] Asymptomatic chlamydia is common among both women and men, and coinfection with *C. trachomatis* often occurs in persons diagnosed with gonococcal infection, especially among men who have sex with men.[20]

Clinical Manifestations

Although often asymptomatic, infection with *C. trachomatis* can cause a wide range of clinical manifestations, including cervicitis, urethritis, epididymitis, proctitis, prostatitis, pelvic inflammatory disease, and neonatal infection.[21] *Chlamydia trachomatis* is the most common cause of nongonococcal urethritis and cervicitis. Chlamydia infections can cause serious complications, especially in women, including pelvic inflammatory disease, ectopic pregnancy, and infertility.

Screening Recommendations

Screening asymptomatic women for chlamydia has been proven to lower overall chlamydial infection rates and to lower the rate of pelvic inflammatory disease.[21] Available data also suggest that persons with HIV who have inflammatory STDs have an increased risk of transmitting HIV, primarily through increased shedding of HIV in the genital tract,[10,11] so routine screening for chlamydia may indirectly reduce the risk of HIV transmission to sex partners. The 2015 CDC STD Treatment Guidelines recommend the following for chlamydia screening in persons with HIV:[21]

- Screen all sexually active individuals for urogenital chlamydia at baseline and at least annually thereafter, depending on the presence of ongoing risk factors and the prevalence of STDs in the community.
- Screen all men who have sex with men for urethral chlamydia as well as for rectal chlamydia if they report receptive anal sex at entry to care and at least annually thereafter. Screening every 3 to 6 months is indicated in men who have sex with men with ongoing risk factors for chlamydia infection.
- Retest 3 months after treatment for chlamydia because of high reinfection rates.
- Routine screening for oropharyngeal chlamydia is not currently recommended, as the clinical significance and transmission risk of chlamydia detected in the oropharynx is not well understood. However, since most commercially available nucleic acid amplification tests (NAATs) are a combination assay that will detect both *N. gonorrhoeae* and *C. trachomatis* from a single specimen, the test results may automatically report the presence of *C. trachomatis*, even if chlamydia oropharyngeal testing was not ordered.[12]
- Routine screening for extragenital chlamydia is not currently recommended in asymptomatic women.

Laboratory Diagnosis

Nucleic acid amplification tests (NAATs)

Nucleic acid amplification tests (NAATs) are the preferred method of testing for *C. trachomatis* due to improved sensitivity and specificity compared to culture.[21] There are multiple NAATs that have FDA clearance for diagnostic testing of chlamydia and gonorrhea in genital samples, including with endocervical swabs, vaginal swabs, urethral swabs, and urine.[12] As of May 23, 2019, the FDA has also cleared two NAATs for diagnostic testing of chlamydia and gonorrhea at extragenital sites (pharynx and rectum; the two tests are the Aptima Combo 2 Assay and the Xpert CT/NG).[13]
Testing for Chlamydia in Women: The optimal NAAT specimen types for detecting *C. trachomatis* urogenital infections in women are vaginal swabs, either self- or clinician-collected. Several studies have shown self-collected vaginal swab specimens perform at least as well as clinician-collected specimens using NAATs and are highly acceptable to women.[14,22,23,24,25] Alternatively, endocervical or first-catch urine samples perform well as screening tests in women, though up to 10% fewer *C. trachomatis* infections may be detected using a urine sample compared with vaginal or endocervical swab.[12,26]

Testing for Chlamydia in Men: In men, the recommended sample type for detecting urogenital *C. trachomatis* infection with a NAAT is a first-catch urine specimen.[12] When screening for chlamydia or gonococcal infections at other sites of exposure, such as the rectum and oropharynx, NAATs are more sensitive and specific than culture.[12] Self-collected rectal swabs demonstrate comparable sensitivity and specificity to clinician-collected swabs when using NAATs, and providing access to self-testing for extragenital infections has been shown to increase screening rates and be highly acceptable to patients.[27,28,29,30]

Culture

Although NAATs are preferred for detection of chlamydia infections in almost all cases, the CDC recommends maintaining laboratory capability to culture chlamydia since culture is the only validated test for use in cases of sexual assault in prepubescent boys and extragenital sites in prepubescent girls, and culture is also important for monitoring trends in antimicrobial susceptibility.

Treatment

According to the 2015 CDC STD Treatment Guidelines, persons with HIV should receive the same treatment for urogenital chlamydia as those without HIV (Table 4).[21] The following summarizes key recommendations in the 2015 CDC STD Treatment Guidelines for the treatment of chlamydia.

- **Uncomplicated Urogenital Chlamydia Infections:** The recommended treatment for uncomplicated genitourinary or rectal chlamydia in nonpregnant individuals is azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days. Studies performed in the general population have shown similar efficacy with azithromycin and doxycycline for urogenital chlamydia infections.[31,32,33] Alternative, less preferable regimens include erythromycin, levofloxacin, or ofloxacin.
- **Rectal Chlamydia Infections:** Currently the 2015 CDC STD Treatment Guidelines recommend treating rectal chlamydia with the same regimens used in urogenital infections. However, a recent retrospective review of observational data involving 1,480 patients, of whom 24% were infected with HIV, suggested that doxycycline was more effective than azithromycin in the treatment of rectal chlamydia.[34] Further study through a randomized control trial is planned to better clarify the optimal treatment of rectal chlamydia.
- **Chlamydia Infections During Pregnancy:** Azithromycin 1 g orally in a single dose is the preferred treatment and alternative regimens include amoxicillin or erythromycin. Doxycycline is contraindicated in pregnant women.
- **Resumption of Sexual Activity:** Persons diagnosed with chlamydia should refrain from sexual intercourse for at least 7 days after receiving a single-dose regimen or after completion of a 7-day regimen. In addition, they should not resume sexual activity until all symptoms related to chlamydia have resolved and their sex partners have received treatment for chlamydia.
- **Management of Sex Partners:** All recent sex partners of persons diagnosed with chlamydia should be contacted and referred for evaluation, testing, and presumptive treatment of chlamydia. Recent is defined in this context as sex contact within the 60 days preceding onset of symptoms or chlamydia diagnosis. In the United States, expedited partner therapy may be considered for men who have sex with women only or women who have sex with men in states where this is allowed by law, and persons diagnosed with chlamydia can deliver therapy to their partners (azithromycin 1 g in a single dose or doxycycline 100 mg orally twice a day for 7 days). The antimicrobial medication must be
accompanied by written materials about possible exposure to chlamydia, the importance of therapy, potential adverse effects of the medications, and the need to seek care for potential complications, including pelvic inflammatory disease. Expedited partner therapy is not recommended for men who have sex with men who are diagnosed with chlamydia due to high risk for coexisting STDs or HIV and lack of data in this population.[8]

- **Follow-up:** Routine test-of-cure after completing therapy for chlamydia is not recommended in nonpregnant individuals, but all women and men diagnosed with chlamydia should return for repeat testing in approximately 3 months due to the substantial risk of reinfection during the period following initial diagnosis and treatment of chlamydia.

- **Oropharyngeal Chlamydia Infections:** Although routine screening for oropharyngeal chlamydia is not recommended, the detection of *C. trachomatis* may be reported when using a NAAT to screen for *N. gonorrhoeae* in the oropharynx. Since available evidence suggests oropharyngeal *C. trachomatis* can be sexually transmitted to genital sites of sexual partners, detection of *C. trachomatis* detected from an oropharyngeal specimen warrants treatment with azithromycin or doxycycline.[21,35,36,37]
Lymphogranuloma Venereum

Introduction

Lymphogranuloma venereum (LGV) is a chronic infection caused by *C. trachomatis* serovars L1, L2, or L3. These serovars are considered more virulent and invasive compared with other *C. trachomatis* serovars. Although LGV is uncommon outside tropical regions, there have been sporadic cases and outbreaks reported in the United States and Europe, particularly among men who have sex with men (MSM), many of whom are also infected with HIV.[38,39,40,41,42]

Clinical Manifestations

LGV often manifests as unilateral tender inguinal or femoral lymphadenopathy, typically following a transient, self-limited genital ulcer or papule at the site of inoculation that often goes unnoticed. In the United States, among men who have sex with men, the classic inguinal adenopathy LGV presentation has become uncommon—LGV more often manifests as proctitis or proctocolitis, with clinical findings that include anal ulcers, anal pain or pruritus, mucoid or hemorrhagic rectal discharge, tenesmus, fever, and/or painful inguinal adenopathy.[43,44] This syndrome can be confused with inflammatory bowel disease, and if not treated early, LGV proctocolitis can progress to chronic colorectal fistulas and strictures.[38,43]

Laboratory Diagnosis

In general, the diagnosis of LGV is made based on clinical suspicion, local epidemiologic data, and testing for *C. trachomatis*, in addition to excluding other etiologies for proctocolitis, inguinal adenopathy, or genital or rectal ulcers. When LGV is suspected, anogenital swabs or lymph node specimens should be sent for *C. trachomatis* culture, direct immunofluorescence, or NAAT in an approved lab. NAATs are the preferred testing method for detecting rectal chlamydia infections.[12,13] If LGV is present, NAAT should be positive for *C. trachomatis*, but commercially available NAATs do not identify which *C. trachomatis* serovar is present. Real-time quadriplex PCR-based assay tests have been developed that can distinguish LGV from non-LGV *C. trachomatis*, but these tests are not commercially available and not approved by the FDA for clinical use.[43,44,45]

Treatment

Presumptive treatment for LGV should be provided prior to the return of lab testing in persons presenting with a clinical syndrome concerning for LGV. The following summarizes the 2015 CDC STD Treatment Guidelines recommendation for the treatment for LGV (Table 5).[44]

- **Recommended Treatment of LGV in Persons with HIV**: The recommended treatment of lymphogranuloma venereum is the same in persons with and without HIV and consists of doxycycline 100 mg orally twice daily for 21 days. In persons with HIV, the treatment response may be delayed and longer courses of therapy may be necessary in some circumstances.[43,44]
- **Management of Sex Partners**: All recent sex partners of persons diagnosed with LGV should be referred for evaluation, testing, and presumptive treatment of chlamydia. Recent is defined as sex contact within the 60 days preceding onset of symptoms or LGV diagnosis. If the sex partner does not have any signs or symptoms that suggest a diagnosis of LGV, then treatment consists of a standard chlamydia regimen (azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice a day for 7 days). If the contact has signs or symptoms that suggest a diagnosis of LGV, then they should receive a 21-day course of doxycycline. Expedited partner therapy is not recommended for contacts of persons diagnosed with LGV.
Syphilis

Introduction

Syphilis is a systemic infection caused by the spirochete Treponema pallidum, referred to as “the great imitator” for its variable clinical manifestations. The natural history of syphilis of untreated syphilis includes a wide range of complications and overlapping disease stages. Although the rates of syphilis declined in the United States in the 1990s, they have increased since 2001 (Figure 3). The increase in syphilis have been most pronounced in men, especially among men who have sex with men. In addition, there were 1,306 cases of congenital syphilis in the United States in 2018, which was a 261% increase from 2013. Coinfection with HIV is common in persons diagnosed with primary and secondary syphilis. Among cases of primary and secondary syphilis in the United States in 2018 for which information about HIV status was known, the percentage with HIV coinfection was 41.6% of the men who have sex with men, 7.9% of men who have sex with women, and 4.0% of women. Syphilis is associated with increased risk of sexual acquisition and transmission of HIV.

Clinical Manifestations

Individuals with HIV typically experience the same stages and physical manifestations of syphilis as persons without HIV, although the stages are more likely to overlap and the symptoms may be more severe.

- **Primary Syphilis**: The manifestation of primary syphilis, if it occurs, is usually within 4 to 8 weeks after an exposure. The most common manifestation of primary syphilis is a firm, painless genital or oral ulcer, which is referred to as a chancre. Persons with HIV who develop primary syphilis may have larger, more numerous chancres that take longer to heal during primary syphilis. If primary syphilis goes untreated, 60 to 90% of persons will develop secondary syphilis (usually within 2 to 8 weeks).

- **Secondary Syphilis**: Secondary syphilis can occur following primary syphilis, but it also can develop in someone who does not have a clinically evident chancre. The manifestations of secondary syphilis often includes a diffuse maculopapular rash on the trunk and extremities (Figure 4) which may involve the palms and soles (Figure 5); flat, mucoid wart-like plaques (condylomata lata) in the folds of the anus and genitals that are often mistaken for anogenital warts; patchy alopecia; lymphadenopathy.

- **Tertiary Syphilis**: Tertiary syphilis develops in up to 25% of untreated syphilis and occurs between 1 and 30 years after initial T. pallidum infection, with multiple possible manifestations, including cardiovascular, neurologic, and cutaneous disease.

- **Neurosyphilis**: The development of neurosyphilis can occur at any stage of T. pallidum infection and a myriad of manifestations can occur, including headache, cranial nerve dysfunction, auditory and visual disturbances, altered mental status, stroke, visual deficits, and loss of vibration sense. The risk of developing neurosyphilis is increased in persons with HIV who have low CD4 counts and high HIV RNA levels. Persons with HIV are more likely to develop uveitis and meningitis compared to persons without HIV.

Screening Recommendations

All sexually active persons with HIV should be screened for syphilis upon initiation of HIV care and at least annually thereafter; more frequent screening is indicated for those with multiple partners, a history of condomless intercourse, a history of sex in conjunction with illicit drug use, or methamphetamine use.

Laboratory Diagnosis

Two categories of serologic tests are required for the presumptive diagnosis of syphilis: (1) nontreponemal tests (e.g. Rapid Plasma Reagin [RPR] and Venereal Diseases Research Laboratory [VDRL]), and (2)...
treponemal tests (e.g. fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* particle agglutination [TP-PA] assay, various enzyme immunoassays [EIAs], and chemiluminescence assays). The use of one test is insufficient for the diagnosis of syphilis due to the limitations of each type of test, so an individual with a positive nontreponemal test should have confirmatory testing with a treponemal-specific test to confirm the diagnosis of syphilis, and vice versa. When serologic findings do not correlate with symptoms of early syphilis, use of other tests (e.g. darkfield microscopy, biopsy with silver staining, and PCR) should be considered. This is especially pertinent for individuals with HIV, since they may have unusual serologic responses.[55] Although the VDRL and RPR are equally valid assays, quantitative results from the two tests cannot be compared directly because RPR titers frequently are slightly higher than VDRL titers.

**Reverse Sequence Syphilis Testing**

Traditionally, the syphilis screening algorithm has consisted of initial screening with a nontreponemal test followed by confirmatory testing of a positive screen with a treponemal test (Figure 6).[50,56] For economic and efficiency reasons, many clinical laboratories now use automated treponemal tests, such as EIAs or chemiluminescence immunoassays as the initial screening test for syphilis, with follow-up testing of positive tests using nontreponemal tests, and have thus reversed the typical syphilis testing sequence (Figure 7).[57] This strategy introduces complexity into interpretation of results, since treponemal tests will identify persons with untreated syphilis, as well as persons who were previously treated for syphilis (since treponemal tests tend to stay positive for life). If a person has a positive treponemal screening test, they should then have a standard nontreponemal test with titer performed reflexively by the laboratory to guide management decisions. If the treponemal test is positive and the confirmatory nontreponemal test is negative (discordant results), a different treponemal test should be reflexively performed to help determine if this is a false-positive test result, early infection, or remote infection (treated or untreated), which must be determined on a case-by-case basis.[57]

**Evaluation for Neurosyphilis**

The 2015 CDC STD Treatment Guidelines recommend performing lumbar puncture and CSF examination in all persons diagnosed with syphilis, regardless of stage or HIV status, if they have neurologic symptoms (altered mental status, ophthalmic or auditory symptoms, cranial nerve abnormalities, stroke, meningitis, or loss of vibratory sensation).[55] In addition, CSF examination is warranted after treatment if any of the following occur: persistent or recurrent symptoms, a sustained fourfold or greater increase in nontreponemal titer, or a lack of fourfold decline in nontreponemal titer within 12 to 24 months of therapy.[55] No single laboratory test can be used to definitively diagnose neurosyphilis in all settings. For example, an elevated CSF white blood count or protein level supports a diagnosis of neurosyphilis, but analysis of CSF cell count is complicated in persons with HIV, as they may have mild mononuclear pleocytosis (and elevated protein levels) due to HIV alone.[55]

Nontreponemal tests (RPR, VDRL) are highly specific for neurosyphilis whereas treponemal tests (FTA-ABS) of the CSF are highly sensitive. A positive CSF VDRL, in the absence of heavy contamination of the CSF with blood, strongly supports a diagnosis of neurosyphilis, whereas a negative CSF FTA-ABS makes the diagnosis of neurosyphilis highly unlikely. If neurosyphilis is suspected but CSF VDRL is negative, obtaining a treponemal test (FTA-ABS) of the CSF can be considered. Among persons with HIV, researchers have identified CD4 count less than 350 cells/mm³ and/or RPR titer of 1:32 or greater as risk factors that may predict neurosyphilis, including among those who are asymptomatic.[58,59] Nevertheless, the 2015 STD Treatment Guidelines note that, in the absence of neurological signs or symptoms, there is no evidence that performing lumbar puncture in this setting improves clinical outcome.[55,58,60]

**Positive Syphilis Test in Asymptomatic Persons**

Asymptomatic persons who have a positive serologic test for syphilis without history of prior syphilis or previous treatment are considered to have latent syphilis. Latent syphilis acquired within the preceding year is called early latent syphilis; all other cases of latent syphilis are either late latent syphilis or latent syphilis of
unknown duration. The diagnosis of early latent syphilis may be made in persons who meet one of the following three criteria: (1) a documented seroconversion or a fourfold or greater increase in titer on a nontreponemal test within the past year, (2) a history of unequivocal symptoms of primary or secondary syphilis within the past year, or (3) a sexual encounter with a partner known to have primary, secondary, or early latent syphilis within the past year. Distinguishing early latent syphilis from late latent syphilis is important since they require different treatment regimens. The following recommendations are based on the 2015 CDC STD Treatment Guidelines.[55]

Treatment

The following summarizes treatment of syphilis in persons with HIV based on the stage and type of syphilis diagnosed (Table 6).[55]

- **Early Syphilis (including primary, secondary, and early latent syphilis):** Treatment of early syphilis is the same for adults with or without HIV and requires a single intramuscular dose of benzathine penicillin G 2.4 million units.[55,61] Studies have demonstrated that enhancing therapy (e.g. adding additional doses of penicillin or other antibiotics) for early syphilis does not improve outcomes.[56] Doxycycline 100 mg orally twice daily for 14 days is considered an alternative for the treatment of early syphilis, but only for nonpregnant persons who have a penicillin allergy. Penicillin is the only known antimicrobial agent that has been shown to be effective in preventing maternal to fetal transmission of syphilis, so pregnant women with a penicillin allergy found to have syphilis infection must undergo penicillin desensitization and receive treatment with penicillin.

- **Late Latent Syphilis or Syphilis of Unknown Duration:** The treatment of late latent syphilis (or latent syphilis of unknown duration) is the same for adults with or without HIV. All individuals with late latent syphilis require three weekly injections of benzathine penicillin G 2.4 million units intramuscularly. Doxycycline 100 mg orally twice daily for 28 days is considered an alternative for the treatment of late latent syphilis, but only for nonpregnant individuals who have penicillin allergy. Pregnant women with syphilis who have a penicillin allergy must undergo penicillin desensitization and receive treatment with penicillin.

- **Neurosyphilis:** Recommended treatment for neurosyphilis consists of aqueous crystalline penicillin G 18 to 24 million units per day (administered as 3 to 4 million units IV every 4 hours or via continuous infusion) for 10 to 14 days. An alternative treatment regimen for neurosyphilis is procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times daily for 10 to 14 days. Since the duration of the neurosyphilis treatment regimen is shorter than treatment of late latent syphilis without neurologic involvement, some experts also recommend giving intramuscular benzathine penicillin G 2.4 million units once weekly for 3 weeks after completion of the neurosyphilis treatment regimen. Treatment for neurosyphilis is the same regardless of HIV serostatus. Treatment of neurosyphilis with agents other than penicillin is not optimal and penicillin desensitization is recommended for penicillin-allergic individuals.

**Monitoring After Treatment for Syphilis (without Neurologic Involvement)**

Although the recommended regimens for syphilis are usually effective, failures can occur.

- **Recommended Monitoring:** All persons with HIV treated for syphilis (without neurologic involvement) should undergo repeat clinical and nontreponemal (VDRL or RPR) serologic testing at 3, 6, 9, 12, and 24 months after treatment.[50] Individuals with HIV who are treated for syphilis often have a slow serologic response after therapy and are more likely to experience serologic failure.

- **Definition of Syphilis Treatment Failure:** Treatment failure is defined as any of the following: (1) signs or symptoms that persist or recur, (2) a sustained (longer than 2 weeks) 4-fold or greater increase in the nontreponemal titer at any point during monitoring, (3) a lack of a 4-fold decline in nontreponemal titers within 12 to 24 months following therapy.[55,62]

- **Treatment Failure Versus Reinfection:** Distinguishing between treatment failure and reinfection can be challenging for individuals who have a poor decline in titer or a good decline followed by a
rebound. In addition, some persons have elevated nontreponemal titers that persist for years (called a “serofast reaction”).

- **Approach to Treatment Failure:** For individuals with HIV who have suspected serologic treatment failure (lack of a 4-fold decline in nontreponemal titers within 12 to 24 months following therapy), a lumbar puncture should be performed and retreatment guided by the CSF results.[55]

- **Persistence of Positive Syphilis Tests:** Most persons with syphilis will have reactive treponemal tests or the remainder of their lives, regardless of treatment or disease activity. Thus, treponemal tests should not be used to assess treatment response.

### Monitoring After Treatment for Neurosyphilis

For persons with HIV who have neurosyphilis, if CSF pleocytosis was present initially, the person should undergo follow-up CSF examination every 6 months until the CSF white blood cell count returns to normal.[55] Some data suggest that CSF abnormalities resolve more slowly among individuals with HIV. If the white blood cell count has not decreased in 6 months or abnormalities persist at 2 years, retreatment should be considered.[55]
Chancroid

Introduction

Chancroid is a relatively common cause of sexually transmitted genital ulcer disease in parts of Africa and the Caribbean and is caused by a small gram-negative rod, *Haemophilus ducreyi*; the disease is endemic mostly in regions of the world with resource-poor health infrastructure and high HIV prevalence. In the United States, chancroid rarely occurs, which creates challenges for recognition and diagnosis of this infection. In 2018, a total of 3 cases of chancroid were reported. Like other sexually transmitted genital ulcer diseases, chancroid may increase the risk of HIV transmission and acquisition. Chancroid in persons with HIV requires close monitoring due to more severe manifestations, higher rates of treatment failure, and delayed healing times.

Clinical Manifestations

Individuals with chancroid often present with one or more painful genital ulcers with yellow or gray exudate, as well as tender inguinal lymph nodes that can progress to fluctuant buboes. In persons with HIV, extragenital involvement of the thighs, anus, abdomen, hands, breast, mouth, and feet can also occur.

Laboratory Diagnosis

Definitive diagnosis of chancroid is made by culturing *H. ducreyi* on specialized culture media, which is neither widely available nor sensitive for detection of the infection. In addition, there are no FDA-approved PCR tests available for *H. ducreyi* (though some laboratories have developed and validated their own PCR tests). A “probable” diagnosis of chancroid can be made if a patient presents with findings suggestive of chancroid (one or more painful genital ulcers and suppurative inguinal lymphadenopathy), and syphilis and herpes simplex virus are ruled out.

Treatment

According to the 2015 CDC STD Treatment Guidelines, persons with HIV should receive the same treatment for chancroid as those without HIV; however, treatment failures and delayed healing of ulcers have been reported in individuals with HIV, and limited data concerning the efficacy of the CDC recommended regimens is available in this population (Table 7). The treatment key recommendations fin the 2015 CDC STD Treatment Guidelines for chancroid are:

- **Treatment Options**: Azithromycin or ceftriaxone are single-dose options for the treatment of chancroid. Additional options include a 3-day course of ciprofloxacin or a 7-day course of erythromycin base.
- **Evaluation of Treatment Response**: Persons diagnosed with chancroid should be reevaluated 3 to 7 days after initiating treatment to ensure clinical and symptomatic improvement. In the absence of evidence of any improvement by 3 to 7 days, alternative diagnoses and antimicrobial resistance should be considered. Persons with HIV should receive very close follow-up after treatment of chancroid, and they may require repeated or longer courses of therapy.
- **Management of Sex Partners**: All very recent sex partners of persons diagnosed with chancroid should be referred for evaluation, testing, and presumptive treatment of chancroid. In this context, very recent is defined as sex& contact within the 10 days preceding onset of symptoms. Expedited partner therapy is not recommended for contacts of persons diagnosed with chancroid.
Herpes Simplex Virus

Introduction

Infections with herpes simplex virus occur frequently in persons with HIV; approximately 60% of persons with HIV are seropositive for HSV-2 and more than 95% test seropositive for either HSV-1 or HSV-2.[66, 67] Recurrent HSV is a chronic infection characterized by periodic reactivation, during which shedding from orolabial and genital mucosal surfaces is increased; shedding can occur even in asymptomatic individuals, and HSV shedding also persists despite highly active antiretroviral therapy among persons coinfected with HSV and HIV.[68, 69, 70, 71] When compared with persons not infected with HIV, individuals infected with HIV tend to have more severe and chronic HSV lesions, and more asymptomatic shedding of HSV-2 in the genital tract.[69] Furthermore, HSV-2 reactivation, including asymptomatic shedding without clinically apparent lesions, can increase the rates of HIV transcription, resulting in increased HIV RNA levels in both plasma and genital tissues, but these changes may be negligible in persons on potent antiretroviral therapy.[72, 73, 74]

Clinical Manifestations

Infection with HSV-1 most often manifests with lesions of the mouth and lips and HSV-2 more commonly causes genital lesions, though HSV-1 and HSV-2 can cause lesions anywhere on the body and are indistinguishable from a clinical perspective. Regardless of the site, persons with genital HSV typically experience a sensory prodrome followed by evolution of the lesion(s) from papule to vesicle to crusting stage.[67] Ulcers caused by HSV tend to be painful, erythematous and have “punched out” borders (Figure 8). Genital HSV lesions may be present on the penis, scrotum, perianal region, and gluteal cleft (Figure 9). If untreated, most persons have symptoms that persist for 5 to 10 days; anti-herpes therapy initiated at onset of the prodrome can shorten the symptomatic period or even abort the outbreak. Individuals with a CD4 count less than 100 cells/mm\(^3\) may have deep, extensive and non-healing ulcers and are more likely to develop acyclovir-resistant HSV if they receive multiple courses of herpes treatment.[67, 75, 76] In addition, persons who have just started effective antiretroviral therapy may develop unusual ulcerative lesions as a manifestation of immune reconstitution syndrome.[69]

Laboratory Diagnosis

The diagnosis of HSV can be difficult on a clinical basis alone and lesions can mimic other infections. Diagnosis, therefore, should be pursued through laboratory testing.[77] Herpes simplex virus DNA PCR testing is the most sensitive method for establishing the diagnosis and the preferred test to use, if available;[77, 78, 79] viral culture and antigen detection are other options.[80] When obtaining clinical samples, the base of the lesion should be scraped to ensure an adequate number of cells are obtained. Serologic testing using an IgG-based assay may be helpful for persons presenting with HSV lesions for the first time.

Screening Recommendations

Serologic screening for HSV-1 and HSV-2 infection is not indicated for the general population, but, based on the interactions between HIV and HSV-2 and the availability of effective suppressive anti-HSV-2 therapy, some experts recommend performing serologic testing for persons with HIV at baseline to identify prior herpes infection.[67, 77, 81]

Treatment

Therapy for Episodic Genital Herpes

Since persons with HIV often have more severe, prolonged cases of orolabial, genital and perianal HSV infections compared to those without HIV, the recommended treatment options in the 2015 CDC STD
Treatment Guidelines and the Adult and Adolescent Opportunistic Infection Guidelines for episodic genital herpes in persons with HIV consist of a 5 to 10-day course of acyclovir, valacyclovir, or famciclovir; intravenous acyclovir may rarely be required for severe mucocutaneous disease (Table 8).[67,77]

Suppressive Therapy for HSV

For persons with HIV who have severe recurrent HSV outbreaks or who want to decrease the frequency of outbreaks, chronic suppressive therapy with valacyclovir, famciclovir, or acyclovir can be effective. Decisions regarding use of suppressive therapy should be made without regard to the individual’s CD4 cell count or changes in CD4 cell count. The 2015 CDC STD Treatment Guidelines recommend acyclovir, valacyclovir, and famciclovir daily as daily suppressive therapy for persons with HIV (Table 9).[77] Numerous studies have shown that suppressive therapy of HSV-2 reduces HIV-1 levels in both the plasma and genital tract.[69,82,83] In a study conducted in Africa that enrolled HIV-1-serodiscordant couples, investigators examined the impact of acyclovir suppressive therapy on HIV transmission for partners who were HSV-2 and HIV-1 positive, but not taking antiretroviral therapy at the time of enrollment; although acyclovir decreased the HIV-1 plasma RNA levels, it did not reduce the risk of HIV transmission.[84] Daily suppressive valacyclovir has been shown to reduce HSV-2 transmission in studies involving heterosexual HSV-serodifferent couples who are not infected with HIV,[85] but similar findings were not observed when using twice-daily acyclovir suppressive therapy in persons with HIV.[86]

Acyclovir-Resistant HSV

Reports have documented rates of resistance to acyclovir in up to 5% of persons with HIV and HSV coinfection,[75] but in recent years, resistance rates have declined. Acyclovir resistance is associated with advanced immunosuppression and frequent use of anti-HSV drugs; repeated episodic therapy poses a greater risk than suppressive therapy. Immunosuppressed individuals with HIV and herpes infection may develop slowly expanding, large ulcerated lesions (Figure 10).[87,88,89] Clinicians should suspect acyclovir resistance when there is no clinical improvement after 7 to 10 days of appropriate HSV treatment. In this situation, a sample from the lesion should be sent for viral culture, with drug susceptibility testing if HSV is isolated. The most common mechanism of acyclovir resistance is absent or decreased production by HSV of the enzyme thymidine kinase (TK- and TK-partial mutants), an enzyme required for the initial step in the triphosphorylation of acyclovir.[89] The preferred treatment for acyclovir-resistant HSV is intravenous foscarnet, but this medication can cause significant adverse effects, including renal and electrolyte abnormalities.[67,87,90] Alternative therapies include topical ophthalmic trifluridine, topical or intravenous cidofovir, and topical imiquimod 5% cream; the topical therapies typically require 21 to 28 days before an adequate response occurs (Table 10).[67]
Human Papillomavirus and Anogenital Warts

Introduction

Anogenital warts, also called condyloma acuminata, are the most common viral STD and are caused by various strains of human papillomavirus (HPV), which is a small double-stranded DNA virus that can be categorized into cutaneous and mucosal groups. Most sexually active adults will acquire HPV infection at some point in their lives, and in most cases the virus is cleared spontaneously. More than 100 types of the human papillomavirus (HPV) have been identified, and a subset (e.g. HPV 16 and 18) has oncogenic potential. Nononcogenic subtypes 6 and 11 cause most genital warts. Men and women with HIV have increased prevalence, greater severity, and persistence of HPV infection.[91,92] In addition, among individuals with HIV, anogenital warts may also be more recalcitrant to therapy due to deficient cell-mediated immunity, particularly in those with advanced immunosuppression.[93,94] Although effective antiretroviral therapy has not been proven to reduce the risk of developing anogenital warts, higher CD4 counts and lower HIV RNA levels seem to independently reduce the risk of developing clinically evident warts.[95] Among men with HIV who have sex with men, younger age and lower HIV RNA have been associated with higher rates of HPV clearance.[96]

Clinical Manifestations

Typical condyloma acuminata are flesh-colored and can range from smooth, flattened lesions to verrucous papules (Figure 11).[94] Most persons with HIV are asymptomatic when initial lesions develop, but some with extensive or multiple lesions may complain of pain, burning, or pruritus. Anogenital warts can appear at multiple sites along the anogenital tract, particularly around the introitus in women, beneath the foreskin of the uncircumcised penis, and on the shaft of the penis in circumcised men.

Screening Recommendations

Use of HPV testing, which detect viral nucleic acid (DNA or RNA) or capsid protein, is recommended as an adjuvant to Pap smears for cervical cancer screening in women aged 30 and older, regardless of HIV status, but should not be used for cervical cancer screening in women younger than age 30, in men, or in individuals with genital warts (or their partners).[93,94] For women younger than age 30 or men who have sex with men (any age), HPV testing is not recommended due to the relatively high prevalence of HPV infection in these populations.[93,94,97] For a full discussion of cervical cancer screening in women and anal cancer screening in men, refer to the Cancer Screening Section in the topic review on Primary Care Management.

Laboratory Diagnosis

The diagnosis of condyloma acuminata is typically made by visual inspection and can be confirmed by biopsy.[94] For lesions that are large, atypical, or refractory to therapy, biopsy with histologic examination is recommended. Persons with external (anal mucosal) warts often have internal warts on the rectal mucosa and thus should have a digital examination or anoscopy. Persons with anal warts should also have a screening test for syphilis because condylomata lata, a manifestation of secondary syphilis, can mimic genital warts caused by HPV. The use of HPV DNA testing for the diagnosis of genital warts is not recommended.[98]

Treatment

The goals of treating warts are amelioration of symptoms (including cosmetic concerns) and removal of the warts; it is unclear whether wart removal reduces future transmission of HPV to sexual partners, and there is no evidence that the presence of genital warts (or their treatment) has any effect on cervical cancer risk in women.[98] Compared to persons without HIV, those with HIV have more treatment-refractory warts and may experience more frequent recurrences.[94] Unfortunately, antiretroviral therapy does not appear to reduce the incidence or prevalence of genital warts, and HPV-related genital and oral disease may persist for years.
through mechanisms of immune reconstitution; oral HPV warts may actually increase after introduction of antiretroviral therapy.\[99,100\] Treatment options in the 2015 CDC STD Treatment Guidelines can be categorized into patient-applied or provider-applied modalities, and they include chemical or physical destruction, immunologic therapy, and surgical therapy; the recommendations for treatment of anogenital warts are the same for persons with or without HIV (Table 11).\[98\]

- Patient-applied options include podofilox 0.5% solution or gel, imiquimod 3.75% cream, imiquimod 5% cream, or sinecatechins 15% ointment.
- Provider-administered treatment options include cryotherapy with liquid nitrogen or cryoprobe, surgical removal, or trichloroacetic acid or bichloroacetic acid 80 to 90% solution.
- Regardless of the treatment method, recurrence rates are high, especially in the first three months after treatment.
- Treatment of internal anogenital warts (meatus, urethral, vaginal, and cervical) is more complicated than external warts and ideally should consist of management by or consultation with a specialist or medical provider who has experience with treating internal anogenital warts (Table 12).\[98\]

**Prevention**

Three HPV vaccines have been approved by the United States FDA: bivalent (2vHPV), quadrivalent (4vHPV), and 9-valent (9vHPV). In the United States, the 9vHPV vaccine is the only HPV vaccine that is currently manufactured. The 9vHPV vaccine is FDA-approved for females and males 9 through 45 years of age.\[101\] The 9-valent HPV vaccine includes seven HPV types protective against cancer (HPV types 16, 18, 31, 33, 45, 52, and 58) and two that protect against HPV-associated warts (HPV types 6 and 11).\[102\] Multiple 4vHPV vaccine studies showed this vaccine to be safe and immunogenic in both males and females with HIV.\[103,104,105\] For persons with HIV, the 9vHPV is recommended for all males and females aged 13 through 26; the 3-dose vaccine schedule should be used for all persons with HIV, regardless of age.\[94,102,106\] For additional details on recommendations for the use of HPV vaccine in persons with HIV, see the Human Papillomavirus Vaccine section in the topic review on Immunizations.
Trichomoniasis

Introduction

Trichomoniasis is the most common nonviral STD worldwide and is caused by the protozoan pathogen *Trichomonas vaginalis*. In the United States, the prevalence of *T. vaginalis* infection among women with HIV is high, with estimates of up to 53%.[107] The epidemiology of *T. vaginalis* among men with HIV is less well characterized, in part because guidelines do not recommend routine screening for *T. vaginalis* in men.[108,109,110] Infection with *T. vaginalis* has been shown to increase HIV transmission risk among both men and women with HIV,[108,111] as well as to increase the risk of HIV acquisition among women.[112]

Clinical Manifestations

Trichomoniasis is usually asymptomatic or minimally symptomatic in most women and men. Women with symptomatic trichomoniasis typically present with diffuse, malodorous, yellow-green discharge and associated vulvar irritation, whereas men may present with symptoms of urethritis.[107,113,114] Trichomoniasis may increase the risk of pelvic inflammatory disease in women with HIV.

Screening Recommendations

Women with HIV should be screened for trichomoniasis at entry to care and annually thereafter.[54,107] Currently, there are no guidelines that recommend screening men for infection with *T. vaginalis*.

Laboratory Diagnosis

A highly sensitive and specific NAAT assay for the detection of *T. vaginalis* is commercially available and is FDA-cleared for use on vaginal, endocervical, or urine specimens in women. If NAAT is unavailable, the diagnosis in women can be made by microscopy of vaginal secretions (wet mount) or by culture, but the sensitivity is much lower than with these methods than with NAAT.[115] For men, NAAT for *T. vaginalis* can be used for urethral swabs and urine samples (as long as validated per CLIA regulations), but one study showed much higher sensitivity with urethral (penile-meatal) swabs.[116] Use of wet mount is not a sensitive test for detecting *T. vaginalis* in men and should not be used; the optimal site and specimen for culture in men is unknown.

Treatment

- **Treatment of Trichomoniasis in Women**: The 2015 CDC STD Treatment Guidelines recommended treatment for trichomoniasis in women with HIV is metronidazole 500 mg orally twice daily for 7 days.[107] This recommendation contrasts with the recommendation for women without HIV (single-dose therapy with either metronidazole 2 g orally or tinidazole 2 g orally).[107,108] The recommendation to use the 7-day course of metronidazole in women with HIV is based on a randomized controlled trial of women with trichomoniasis and HIV that found single dose therapy with metronidazole 2 g to be less effective than a 7-day metronidazole course, based on reevaluation 1 to 2 weeks after treatment and 3 months after treatment.[117]
- **Treatment of Trichomoniasis in Men**: The recommended treatment of trichomoniasis in men with HIV is metronidazole 2 g or tinidazole 2 g in a single dose; no trials have yet examined the efficacy of single-dose therapy compared to multi-dose metronidazole therapy for trichomoniasis in men with HIV. Rescreening 3 months after treatment for trichomoniasis is recommended in women with HIV, but not for men with HIV.[54,107]
Additional Topics

Cervicitis

Cervicitis can result from common STDs, including gonorrhea, chlamydia, trichomoniasis, and genital herpes. The diagnosis and treatment of cervicitis in women with HIV is the same as in those without HIV. Treatment of cervicitis in women with HIV has additional importance since cervicitis increases HIV genital shedding and may increase the risk of HIV transmission to sexual partners.[118] Evolving drug resistance is a significant threat to the treatment of *N. gonorrhoeae* and *T. vaginalis*, and there are case reports of azithromycin-resistant *C. trachomatis*, but there have not been any cases of confirmed *in vivo* resistance in *C. trachomatis* to either azithromycin or doxycycline.[119]

- **Recommended Treatment**: The recommended empiric treatment of cervicitis consists of either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice daily for 7 days; concurrent treatment for gonococcal infection should be considered if the person is at risk for gonorrhea or lives in a community where the prevalence of gonorrhea is high.[118] In women with persistent cervicitis, if reinfection is ruled out and treatment failure is considered improbable, it is reasonable to consider alternative diagnoses, keeping in mind that no etiologic agent is found in more than half of all cases of cervicitis.[118,120] Repeating initial therapy, or treating with a longer course of standard therapy, has not been established to improve response rates in persistent cervicitis. The clinical course and treatment recommendations for cervicitis are the same for women with or without HIV.

Persistent Urethritis

Persons with recurrent or persistent symptoms of urethritis following appropriate therapy for nongonococcal urethritis should be reevaluated; this is particularly important for persons with HIV, as nongonococcal urethritis may increase the risk of HIV transmission to sex partners.[118] Possible causes for persistent symptoms despite appropriate antibiotic therapy include reinfection, lack of adherence to initial course of treatment, infection with a resistant organism, or infection with a secondary pathogen; one study found that persistent *C. trachomatis* and *M. genitalium* were common after initial therapy for urethritis, especially in patients who fail doxycycline therapy.[121]

- **Recommended Treatment**: For persons who did not comply with their initial treatment or had reexposure to an untreated sex partner, the same regimen they initially received can be used for retreatment. If a person was compliant with the initial regimen and reexposure did not occur, then retreatment should consist of moxifloxacin 400 mg once daily for 7 days.[118] In areas of high prevalence of *Trichomonas vaginalis*, men who have sex with women and have persistent urethritis should be treated with a single oral dose of either 2 g of metronidazole or 2 g of tinidazole; in addition, for men initially treated with doxycycline, retreatment should include azithromycin as a single 1 g dose.[118] The diagnosis of prostatitis should be considered in male patients with persistent urethritis symptoms.

Epididymitis

Treatment of uncomplicated epididymitis is the same in all men regardless of HIV status, and should be aimed at the most likely organisms. Men younger than age 35 typically have epididymitis secondary to *Chlamydia trachomatis* and *N. gonorrhoeae* infection, whereas men older than age 35 are at increased risk for non-sexually transmitted epididymitis associated with urinary tract instrumentation or surgery. Men who practice insertive anal intercourse are also at risk for developing epididymitis from enteric organisms, such as *Escherichia coli*. In men with HIV, several organisms have been identified that can rarely cause of epididymitis, including cytomegalovirus, *Salmonella*, *Toxoplasma gondii*, *Ureaplasma urealyticum*, *Corynebacterium* sp., *Mycobacterium* sp., and *Mima polymorpha*, fungal infections, and mycobacteria.[122]
• **Recommended Treatment:** Treatment of *Chlamydia trachomatis* and *N. gonorrhoeae* infection is recommended in persons with epididymitis. In persons at risk for enteric organisms, a fluoroquinolone should be given in addition to treatment for sexually transmitted *C. trachomatis* and *N. gonorrhoeae*. [122, 123, 124]

### Proctitis

The most common infectious etiologies of proctitis are *C. trachomatis* (including subtypes that cause LGV), *N. gonorrhoeae, T. pallidum*, and herpes simplex virus.[125] Diagnosis should be made by visual inspection (via anoscopy or sigmoidoscopy), stool examination, and culture.

• **Recommended Treatment:** Empiric therapy for *C. trachomatis* and *N. gonorrhoeae* with ceftriaxone 250 mg in a single intramuscular dose plus doxycycline 100 mg orally twice a day for 7 days should be initiated empirically if an anorectal exudate is identified or polymorphonuclear leukocytes are detected on Gram stain of anorectal secretions.[125] Individuals with HIV may have unusual or more severe clinical findings, such as bloody discharge, perianal ulcers, or mucosal ulcers, and all persons with HIV who have proctitis should be presumptively treated for both HSV and LGV (regardless of other clinical symptoms).[125]

### Mycoplasma genitalium

Recently, increasing attention has been given to *Mycoplasma genitalium* as a possible cause for persistent or recurrent cervicitis and urethritis. In January 2019, the FDA authorized use of and marketing of the Aptima *Mycoplasma genitalium* Assay for diagnosing *M. genitalium;* this nucleic acid amplification test (NAAT) is the first FDA-approved test of any kind for *M. genitalium.* The sensitivity for this test is approximately 90% in vaginal, male urethral, and male urine samples. The sensitivity was relatively lower in female urine (77.8%) and endocervical samples (81.5%). The specificity if this test was very high, ranging from 97.8 to 99.6%, depending on the sample and the study. The optimal treatment of *M. genitalium* is unknown.[126]

• **Recommended Treatment:** The optimal initial therapy for *M. genitalium* is not clear. Available data suggest azithromycin is significantly better than doxycycline.[126] Treatment with moxifloxacin has shown good results for persons with *M. genitalium* who failed initial therapy.
Multiple studies document synergy between HIV and sexually transmitted diseases: HIV can increase the incidence, severity, and persistence of many infections, and STDs can increase the risk of sexual acquisition of HIV and enhance the transmission of HIV.

Men and women with HIV should have screening for chlamydia, gonorrhea, and syphilis at baseline and periodically thereafter, depending on ongoing risk factors. Women with HIV should also be tested for trichomoniasis at baseline and periodically thereafter.

The recommended treatment regimens for chlamydial in persons with HIV consist of either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days.

Lymphogranuloma venereum, an infection caused by *C. trachomatis* serovars L1, L2, L3, is characterized by painful inguinal adenopathy, anal ulcers, and rectal symptoms. The recommended treatment of LGV in persons with HIV is doxycycline 100 mg orally twice daily for 21 days.

The recommended treatment regimen for gonococcal infections is a single dose of intramuscular ceftriaxone 500 mg, with or without oral doxycycline 100 mg twice daily for 7 days, depending on whether chlamydia infection has been ruled out. Pregnant persons should receive a single 1 gram oral dose of azithromycin instead of doxycycline.

Treatment for syphilis depends on the duration of infection and whether neurosyphilis is suspected or documented. Individuals with HIV who are treated for syphilis require serologic follow-up for 24 months after completion of therapy.

For treatment of trichomoniase in women with HIV, a 7-day course of oral metronidazole treatment is more effective than single-dose metronidazole therapy; data is lacking on the appropriate screening, testing and treatment options for trichomoniase in men with HIV infection.

Chancroid infection is rare in the United States, and treatment experience is limited in persons with HIV; among individuals with HIV infection, chancroid disease course tends to be more severe and prolonged, and treatment failure rates are higher.

Individuals with HIV tend to have more severe and chronic herpes simplex lesions, and more asymptomatic shedding of HSV-2 in the genital tract, compared to patients not infected with HIV; suppressive therapy with valacyclovir 500 mg twice daily should be considered in persons with HIV.

Genital warts caused by human papillomaviruses are common among individuals with HIV. Treatment is aimed at ameliorating symptoms, and the 9-valent HPV vaccine protects against HPV subtypes 6 and 11, which cause approximately 90% of genital warts.
Citations


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47. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Syphilis. Last updated: December 17, 2015.


61. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in


**References**


Figures

Figure 1 Gonorrhea—Rates of Reported Cases by Age Group, United States, 2018

Figure 2 Chlamydia—Rates of Reported Cases by Sex and Age Group, United States, 2018


*Per 100,000 population
Figure 3 Syphilis Cases, All Stages of Infection, United States, 2000-2018

Figure 4 Diffuse Erythematous Maculopapular Lesions in Man with HIV and Secondary Syphilis

Photograph from David H. Spach, MD
Figure 5 Papular Lesions on Hand of Man with HIV and Secondary Syphilis

Photograph from David H. Spach, MD
Figure 6 Syphilis Serologic Screening—Traditional Sequence Algorithm

The traditional (standard) serologic screening sequence algorithm uses a quantitative nontreponemal test (RPR or VDRL) for screening followed by a treponemal test for confirmation of positive screening tests. Abbreviations: RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = Treponema pallidum particle agglutination.
Figure 7 Syphilis Serologic Screening—Reverse Sequence Algorithm

The reverse serologic screening algorithm uses an initial treponemal test for screening, followed by a nontreponemal test confirmation. A specimen with reactive EIA/CIA results should be tested reflexively with a quantitative nontreponemal test (RPR or VDRL). Abbreviations: EIA = enzyme immunoassay; CIA = chemiluminescence immunoassays; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = Treponema pallidum particle agglutination.

Figure 8 Multiple Ulcerated Lesions on the Scrotum of Man with AIDS and CD4 Count Less than 50 cells/mm$^3$

Chronic ulcerative lesions caused by herpes simplex virus infection are much more common in persons with HIV if they have a CD4 count less than 100 cells/mm$^3$

Photograph from David H. Spach, MD
Figure 9 HSV Lesion in Gluteal Cleft

The black arrow denotes the ulcerated lesion with exudate in the gluteal cleft.

Photograph from David H. Spach, MD
Figure 10 Acyclovir-Resistant HSV Lesion in Gluteal Fold

This man with advanced AIDS developed a slowly expanding ulcerating lesion in the upper region of the gluteal cleft.
Figure 11 Multiple Warts on Shaft of Penis in Man with HIV

Photograph from David H. Spach, MD
Table 1.

**STD Screening Recommendations in Persons with HIV**

<table>
<thead>
<tr>
<th>STD</th>
<th>Screening Indications and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
<td>• For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter</td>
</tr>
<tr>
<td></td>
<td>• More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>• For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter</td>
</tr>
<tr>
<td></td>
<td>• More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology</td>
</tr>
<tr>
<td>Syphilis</td>
<td>• For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter</td>
</tr>
<tr>
<td></td>
<td>• More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>• Recommended for sexually active women at entry to care and at least annually thereafter</td>
</tr>
<tr>
<td>Herpes</td>
<td>• Type-specific HSV serologic testing should be considered for persons presenting for an STD</td>
</tr>
</tbody>
</table>
| STD | Screening Indications and Frequency evaluation  
<table>
<thead>
<tr>
<th></th>
<th>(especially for those persons with multiple sex partners), persons with HIV infection, and men who have sex with men at increased risk for HIV acquisition</th>
</tr>
</thead>
<tbody>
<tr>
<td>hepatitis B</td>
<td>• Test for HBsAg and anti-HBc and/or anti-HBs at entry to care</td>
</tr>
</tbody>
</table>
| hepatitis C | • Serologic testing at initial evaluation  
|     | • Annual HCV testing in men who have sex with men |

**NOTE:** This table is based on recommendations in the 2015 Sexually Transmitted Diseases Treatment Guidelines

**Source:**

Table 10. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Treatment of Acyclovir-Resistant Mucocutaneous HSV Infection

**Preferred Therapy**

- Foscarnet 80-120 mg/kg/day IV in 2–3 divided doses until clinical response (AI)

**Alternative Therapy (Duration: 21-28 days or longer, based on clinical response) (CIII):**

- Topical trifluridine, or
- Topical cidofovir 1% gel, or
- Topical imiquimod 5% cream three times/week, or
- IV cidofovir 5 mg/kg IV once weekly

**Note**

- Topical formulations of trifluridine and cidofovir are not commercially available
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir.

HSV = herpes simplex virus; IV = intravenously

**Rating System for Prevention and Treatment Recommendations**

- Strength of Recommendation: A = Strong; B = Moderate; C = Optional
- Quality of Evidence for the Recommendation: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Herpes simplex virus. Last updated: May 26, 2020. [HIV.gov]