Sexually Transmitted Infections

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Module 4: Co-Occurring Conditions
Lesson 4: Sexually Transmitted Infections

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Overview

Sexually transmitted diseases (STDs) incorporate a variety of clinical syndromes caused by sexually transmitted infections (STIs) that may be acquired and transmitted through sexual activity.[1] Among persons with HIV, the diagnosis and treatment of STIs is important for three main reasons: (1) STIs are common, (2) HIV can potentially impact the severity and response to the treatment of STIs, and (3) development of STIs can impact the transmission of HIV.[2,3,4,5] Despite education and prevention efforts, national trends indicate a rising incidence of several STIs, especially among men with HIV who have sex with men.[6] Clinicians providing care to persons with HIV play a crucial role in STD prevention through regular risk assessment and counseling, immunization for vaccine-preventable STIs, routine screening, diagnosis and treatment of STIs, and partner services. This Topic Review will explore screening, diagnosis, and treatment strategies for the most common and important STIs that occur among persons with HIV; the recommendations herein are based primarily on the 2021 STI Treatment Guidelines.[1] For more detailed discussions on STIs, see the 2021 Sexually Transmitted Infections Treatment Guidelines and the National STD Curriculum.

Screening for STIs in Persons Living with HIV

In order to adequately address the ongoing burden of STIs 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). The highest priority for screening is to test for common curable STIs, including chlamydia, gonorrhea, and syphilis, in men and women, as well as trichomoniasis in women. In sexually active persons with HIV, screening for these STIs 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 STIs, exchanging sex for money or drugs, engaging in sex with a new 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 STIs. The following table outlines the 2021 STI Treatment Guidelines recommendations for STI screening in persons with HIV.[1](Table 1)

Gonococcal Infections

Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative intracellular diplococcus. Gonorrhea is the second most common bacterial STI in the United States, with 601,319 cases reported in the United States in 2023.[6] Gonorrhea is most often diagnosed in younger adults, especially individuals 20 to 29 years of age (Figure 1).[6]

Clinical Manifestations

Similar to *Chlamydia 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 or pustular skin rash, septic arthritis, tenosynovitis, and occasionally perihepatitis, endocarditis, and meningitis. Urethral infection is typically symptomatic, but pharyngeal and anorectal infection with *N. gonorrhoeae* often occurs without causing symptoms.

Screening Recommendations

The 2021 STI Treatment Guidelines recommend the following for gonorrhea screening in persons with HIV:[7,8]

- Screen all sexually active persons at baseline and at least annually thereafter, with the frequency depending on the presence of ongoing risk factors and the prevalence of sexually transmitted infections in the community.
- Screen all men who have sex with men every 3 to 6 months.
- Screen all sites of anatomic exposure; this may include screening for urethral, rectal, and pharyngeal gonorrhea.

Laboratory Diagnosis

Nucleic acid amplification tests (NAATs) are the preferred diagnostic tests for *Neisseria gonorrhoeae*, primarily due to superior sensitivity when compared with culture.[1,9] These tests can be used for gonorrhea diagnostic testing of urine samples and on swabs obtained from the endocervix, vagina, urethra, pharynx, and rectum.[7,9] These tests can be used to detect *N. gonorrhoeae* during routine screening and for diagnosing a symptomatic gonococcal infection. When testing, collect samples from all sites of anatomic exposure, including genital, rectal, and pharyngeal sites. Many clinics now use self-collection due to improved clinic flow and patient preference; self-collected specimens perform as well as clinician-collected samples for detection of *N. gonorrhoeae*.[9,10,11,12] Note that for women, a first-catch urine sample detects approximately 10% fewer cases of *N. gonorrhoeae* infections compared with vaginal or endocervical swabs.[9] A Gram's stain of a urethral or cervical discharge specimen demonstrating the presence of leukocytes with intracellular gram-negative diplococci is highly specific for *N. gonorrhoeae* urethral infection, but should not be used to rule out *N. gonorrhoeae* infection due to lower sensitivity.[7]

Treatment

The following summarizes recommendations in the 2021 STI Treatment Guidelines for the treatment of individuals with gonococcal infections; the treatment is the same for persons with or without HIV.[7] Two new antimicrobials, gepotidacin and zoliflodacin, have recently been FDA-approved for the treatment of gonorrhea. These antimicrobials are not included in the guidelines, but they provide additional options for the treatment of cephalosporin-resistant gonorrhea and for persons with gonorrhea who are allergic to cephalosporins.

- **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 doxycycline 100 mg orally twice daily for 7 days, depending on whether chlamydia infection has been ruled out. For persons who weigh 150 kg or more, the ceftriaxone dose is 1 g as a single intramuscular dose. If chlamydia has not been ruled out, then doxycycline 100 mg orally twice daily for 7 days should also be given. If chlamydia treatment is needed and the patient is a pregnant woman, azithromycin 1 g orally as a single dose is recommended instead of doxycycline. Alternative regimens are listed in the table below.

2021 STI Treatment Guidelines: Gonococcal Infections
Table 2. Treatment of Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum

Recommended **Regimen if Chlamydial Infection Excluded**

Ceftriaxone

Ceftriaxone

Tradename:Rocephin

500 mg* IM in a single dose for persons weighing <150 kg

Note: *For persons weighing ≥150 kg, ceftriaxone 1 g IM should be administered.

Recommended **Regimen if Chlamydial Infection Has Not Been Excluded**

Ceftriaxone

Ceftriaxone

Tradename:Rocephin

500 mg* IM in a single dose for persons weighing <150 kg

Doxycycline

Doxycycline

Tradename:Doryx, Vibramycin

100 mg orally twice daily for 7 days+

During pregnancy, oral azithromycin 1 gram in a single dose is recommended to treat chlamydia.

Note: *For persons weighing ≥150 kg, ceftriaxone 1 g IM should be administered.

Alternative **Regimen if Ceftriaxone is Not Available**

Gentamicin

Gentamicin

Tradename:Garamycin

240 mg IM in a single dose

Azithromycin

Azithromycin

Tradename:Zithromax

2 g orally in a single dose+

Alternative **Regimen if Ceftriaxone is Not Available**

Cefixime

Cefixime

Tradename:Suprax

800 mg orally in a single dose

Note: If treating with cefixime, and chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally twice daily for 7 days. During pregnancy, oral azithromycin 1 g in a single dose is recommended to treat chlamydia.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Gonococcal infections. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

- **Treatment of Uncomplicated Gonococcal Infection of the Pharynx**: For uncomplicated gonococcal infections of the pharynx, the same treatment regimen is recommended as for treating 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 7 to 14 days after treatment, regardless of the treatment regimen. The rationale for this recommendation is that *N. gonorrhoeae* is more difficult to eradicate in the oropharynx than at urogenital sites.

2021 STI Treatment Guidelines: Gonococcal Infections
Table 3. Treatment of Uncomplicated Gonococcal Infection of the Pharynx

Recommended **Regimen**

Ceftriaxone

Ceftriaxone

Tradename:Rocephin

500 mg* IM in a single dose for persons weighing <150 kg

If chlamydial infection is identified when pharyngeal gonorrhea testing is performed, treat with doxycycline 100 mg orally 2 times a day for 7 days; women who are pregnant should receive azithromycin 1 g orally in a single dose (instead of doxycycline).

Note: *For persons weighing ≥150 kg, ceftriaxone 1 g IM should be administered.

No reliable alternative treatments are available for pharyngeal gonorrhea. For persons with a history of a beta-lactam allergy, a thorough assessment of the reaction is recommended. For persons with an anaphylactic or other severe reaction (e.g., Stevens Johnson syndrome) to ceftriaxone, consult an infectious disease specialist for an alternative treatment recommendation.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Gonococcal infections. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

- **Persons with Penicillin Allergy**: The management of persons with penicillin allergy is complicated since fewer than 10% of persons who self-report a penicillin allergy have a positive skin test with penicillin allergy testing. In addition, fewer than 1.0% of persons with penicillin allergy will have an allergic reaction to a third-generation cephalosporin, such as ceftriaxone or cefixime. Thus, most persons with a penicillin allergy can receive ceftriaxone therapy for the treatment of gonorrhea. 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.[13]

Counseling and Follow-Up

- **Resumption of Sexual Activity**: Persons diagnosed with gonorrhea should refrain from sexual activity for at least 7 days after receiving treatment, symptoms have resolved, and all sex partners have been treated.
- **Management of Sex Partners**: All recent (within the prior 60 days) sex partners of persons diagnosed with gonorrhea should be referred for evaluation, testing, and presumptive treatment for gonorrhea. If the person diagnosed with gonorrhea did not have chlamydia excluded, then the sex partner should also receive treatment for chlamydia. If there were no sexual contacts in the prior 60 days, then the most recent prior sex partner should receive evaluation and treatment.
- **Follow-Up Testing**: Retesting in 3 months is indicated for all persons diagnosed with gonorrhea because of high reinfection rates. Routine test-of-cure is not recommended for persons diagnosed with gonorrhea from the cervix, urethra, or rectum. All persons diagnosed with pharyngeal gonorrhea should have a routine test-of-cure 10 to 14 days after completing treatment, regardless of the treatment regimen.

Chlamydial Infections

Chlamydia trachomatis is the most commonly reported STI in the United States, with 1,648,568 reported cases in 2023.[6] Among the reported cases, based on sex assigned at birth, 63% were females; the highest number of cases and rates were in females under the age of 25 years, particularly females 20 to 24 years of age (Figure 2).[6] 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.[14]

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.[15] *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. 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. In the United States, recent outbreaks and sporadic cases of LGV among men who have sex with men (with high rates of HIV) have predominantly manifested as proctocolitis, with clinical findings that include anal ulcers, anal pain or pruritus, mucoid or hemorrhagic rectal discharge, tenesmus, and fever.[16,17]

Screening Recommendations

The 2021 STI Treatment Guidelines recommend the following for chlamydia screening in people with HIV.[15]

- 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 STIs in the community.
- Screen all men who have sex with men for chlamydia on entry to care and then every 3 to 6 months if they are sexually active. More frequent screening may be indicated based on the presence of ongoing risk of acquiring STIs and the prevalence and incidence of STIs in the community.
- 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. 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.
- All pregnant women who are younger than 25 years of age should undergo screening for chlamydia infection at the first prenatal visit and again during the third trimester to prevent fetal complications due to chlamydia. These screening recommendations also apply to pregnant women older than 25 years of age who are at increased risk of acquiring chlamydia, including women with new or multiple sex partners, a sex partner who concurrently has other sex partners, or a sex partner who has an STI.

Laboratory Diagnosis

Nucleic acid amplification tests are the preferred method of testing for *C. trachomatis* due to improved sensitivity and specificity compared to culture.[15] These tests can be used for diagnostic testing of chlamydia and gonorrhea in urine samples and on swabs obtained from the endocervix, vagina, urethra, and rectum.[9] In addition, NAATs can be used for routine screening and for diagnosis of a symptomatic chlamydial infection. When testing, collect samples from all sites of anatomic exposure; this may include specimens for genital and rectal sites. Many clinics now use self-collection due to improved clinic flow and patient preference; self-collected swab specimens perform as well as clinician-collected samples for detecting

C. trachomatis. Note that for women, a first-catch urine sample detects approximately 10% fewer cases *C. trachomatis* urogenital infections compared with vaginal or endocervical swabs.[9,18] Routine laboratory NAAT testing for chlamydia does not identify specific LGV serovars.

Treatment

The following summarizes recommendations in the 2021 STI Treatment Guidelines for the treatment of urogenital chlamydial infections; the treatment is the same for individuals with or without HIV.[15]

- **Uncomplicated Urogenital Chlamydial Infections**: The recommended treatment for uncomplicated genitourinary or rectal chlamydia in nonpregnant adults is doxycycline 100 mg orally twice a day for 7 days. Alternative, less preferable regimens include azithromycin 1 gram orally as a single dose or levofloxacin 500 mg orally once daily for 7 days. The recommendation for doxycycline as the preferred treatment for chlamydia is based on two randomized, double-blind clinical trials that showed a 7-day course of doxycycline was superior to single-dose azithromycin for the treatment of asymptomatic rectal chlamydial infections among men who have sex with men.[19,20] Studies performed in the general population have shown similar efficacy with azithromycin and doxycycline for urogenital chlamydia infections.[20,21]

2021 STI Treatment Guidelines: Chlamydial Infections
Table 4. Treatment of Chlamydial Infections Among Adolescents and Adults

Recommended **Regimen**

Doxycycline

Doxycycline

Tradename:Doryx, Vibramycin

100 mg orally twice a day for 7 days

Alternative **Regimens**

Azithromycin

Azithromycin

Tradename:Zithromax

1 g orally in a single dose

Alternative **Regimens**

Levofloxacin

Levofloxacin

Tradename:Levaquin

500 mg orally once daily for 7 days

Note: Doxycycline is also available in a more costly delayed-release 200-mg tablet formulation, which requires once-daily dosing for 7 days and is equally effective as doxycycline 100 mg twice daily for 7 days for treating urogenital chlamydial infection in men and women.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Chlamydial infections. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

- **Chlamydial Infection During Pregnancy**: Azithromycin 1 g orally in a single dose is the preferred treatment during pregnancy; the alternative regimen in pregnancy is amoxicillin 500 mg orally three times daily for 7 days. Doxycycline is not recommended for the treatment of chlamydial infection during pregnancy due to its negative effects on fetal tooth and bone development.
- **Oropharyngeal Chlamydia Infections**: Although routine screening for oropharyngeal chlamydial infection 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 sex partners, detection of *C. trachomatis* detected from an oropharyngeal specimen warrants treatment with doxycycline in nonpregnant adults and azithromycin in pregnant women.[15,22,23,24]
- **LGV**: For nonpregnant individuals, the recommended treatment for LGV consists of doxycycline 100 mg orally twice daily for 21 days.[25] For pregnant women, there are limited data, but most experts would recommend using oral azithromycin 1 gram once weekly for 3 weeks.

Follow-Up

- **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. In this context, “recent” is defined as sexual contact within the 60 days preceding onset of symptoms or chlamydia diagnosis. If no sexual contact has occurred in the 60 days before the diagnosis of chlamydia or onset of symptoms, then the most recent sex partner prior to that 60-day period should be evaluated and presumptively treated for chlamydial infection.

- **Follow-Up**: Routine test-of-cure after completing therapy for chlamydia is not recommended in nonpregnant individuals, but all persons 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. All women treated for chlamydial infection during pregnancy should have a test-of-cure performed 4 weeks after completing therapy, as well as repeat testing 3 months after treatment to test for reinfection.

Syphilis

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 untreated syphilis includes a wide range of complications and overlapping disease stages. In 2023, there were 209,253 cases of syphilis reported in the United States, including 3,882 cases of congenital syphilis.[6] Although the number of syphilis cases declined in the United States in the 1990s, there has been an overall major increase since the year 2000 (Figure 3).[6] In the last 5 years, syphilis cases in the United States increased 61%.[6] The increase in syphilis cases has been most pronounced in men, especially among men who have sex with men, but major increases have also occurred in women in recent years.[6] Coinfection with HIV is common in persons diagnosed with primary and secondary syphilis.[6] Among cases of primary and secondary syphilis in the United States in 2023 for which information about HIV status was known, the percentage of HIV coinfection was 41.0% among men who have sex with men, 6.5% of men who have sex with women, and 4.1% of women.[6] Syphilis is associated with an increased risk of sexual acquisition and transmission of HIV.[6,26]

Clinical Manifestations and Stages of Syphilis

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 and/or multiple chancres that take longer to heal during primary syphilis.[26] 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 can also develop in someone who does not have a clinically evident chancre. The manifestations of secondary syphilis often include a diffuse maculopapular rash on the trunk and extremities (which may involve the palms and soles); flat, mucoid wart-like plaques (condylomata lata) in the folds of the anus and genitals that are often mistaken for anogenital warts; patchy alopecia; and lymphadenopathy (Figure 4).[26,27,28]
- **Latent Syphilis**: Asymptomatic persons who have a positive serologic test for syphilis without a 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.
- **Tertiary Syphilis**: Tertiary syphilis develops in up to 25% of untreated syphilis and occurs between 1 and 30 years after the initial *T. pallidum* infection, with multiple possible manifestations, including cardiovascular, neurologic, and cutaneous (gummatous) disease.
- **Neurosyphilis, Ocular Syphilis, and Otosyphilis**: The development of neurosyphilis, ocular syphilis, and otosyphilis can occur at any stage of *T. pallidum* infection. Persons with HIV and neurosyphilis can present with a myriad of manifestations, 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.[29,30,31] Persons with HIV are more likely to develop uveitis and meningitis compared to persons without HIV.[26] Ocular syphilis and otosyphilis can develop independently of neurosyphilis. People with ocular syphilis most often present with uveitis, but any portion of the eye can be involved; those with otosyphilis most often present with sensorineural hearing loss.[28]

Screening Recommendations

All sexually active persons with HIV should be screened for syphilis upon initiation of HIV care and at least annually thereafter.[8,28] 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.[8,9,28]

Laboratory Diagnosis

Two categories of assay are used when attempting to make a serologic diagnosis of syphilis: treponemal and nontreponemal tests.

- **Treponemal Tests**: The treponemal tests used in the United States include the enzyme immunoassay (EIA), chemiluminescence assay (CIA), *Treponema pallidum* particle agglutination (TP-PA) assay, and the fluorescent treponemal antibody absorbed (FTA-ABS) test. The EIA and CIA are typically used for an initial screening test, whereas the TP-PA and FTA-ABS are usually used as a confirmatory test. Results with all treponemal tests are qualitative (reactive or nonreactive).
- **Nontreponemal Tests**: The nontreponemal tests used in the United States include the Rapid Plasma Reagin (RPR) and Venereal Diseases Research Laboratory (VDRL) assays. The RPR and VDRL assays provide qualitative results (reactive or nonreactive) and quantitative results (titers). Although the RPR and VDRL are equally valid assays, quantitative results from the two tests are not equivalent and should not be compared directly. The nontreponemal tests are used for initial screening, monitoring response to treatment (based on decreases in titers), and for diagnosing new syphilis infection in a person with prior treated syphilis (based on increases in titers).

Traditional and Reverse Sequence Syphilis Testing Algorithms

For persons without a prior diagnosis of syphilis, there are two screening algorithms commonly used: the reverse sequence algorithm and the traditional algorithm (Figure 5).[28,32] Both are considered acceptable and the choice of which algorithm to use varies by regional laboratory protocols and preferences. Note that for a person with a known prior diagnosis of syphilis, screening for syphilis reinfection should use the nontreponemal test (RPR or VDRL), with all reactive tests reflexed to a quantitative RPR or VDRL titer. Treponemal tests typically remain reactive for life, even after successful syphilis treatment. Thus, if a person has a positive treponemal EIA test, a nontreponemal test (with a titer) should then be performed reflexively by the laboratory to guide management decisions.

- **Reverse Sequence Algorithm**: The reverse screening starts with a screening treponemal test (EIA or CIA) with reactive tests usually automatically reflexing to a nontreponemal test (RPR or VDRL) with quantitation (titer).[33] If the initial treponemal test is reactive and the confirmatory nontreponemal test is nonreactive (discordant results), a second and different treponemal test (usually TP-PA or FTA-ABS) should be reflexively performed to help determine on a case-by-case basis whether this is a false-positive test result, early infection, or remote infection (treated or untreated).[33]
- **Traditional Algorithm**: The traditional algorithm starts with a nontreponemal test (RPR or VDRL) followed by confirmatory testing of a reactive screen with a confirmatory treponemal test (usually TP-PA or FTA-ABS).[28,32,34]

Evaluation for Neurosyphilis

Persons with syphilis who have new neurologic signs or symptoms should undergo lumbar puncture and cerebrospinal fluid (CSF) examination, regardless of syphilis stage or HIV status.[28] Common neurosyphilis manifestations include altered mental status, cranial nerve abnormalities, stroke, meningitis, or loss of vibratory sensation.[28] Persons with ocular syphilis or otosyphilis do not require CSF examination, unless they have concomitant neurologic symptoms or signs. No single laboratory test can be used to definitively diagnose neurosyphilis in all settings. For example, an elevated CSF white blood count (greater than10

cells/mm^3) or elevated protein level (greater than 45 mg/dL) supports a diagnosis of neurosyphilis, but should not be viewed as definitive.[28] The nontreponemal CSF VDRL test is highly specific for a neurosyphilis diagnosis, whereas the treponemal CSF tests (FTA-ABS or TP-PA) are highly sensitive. Thus, a reactive CSF VDRL, in the absence of heavy contamination of the CSF with blood, strongly supports a diagnosis of neurosyphilis, whereas a nonreactive CSF FTA-ABS (or TP-PA) makes the diagnosis of neurosyphilis highly unlikely.[28,35,36]

Treatment

The following summarizes treatment of syphilis in persons with HIV based on the stage and type of syphilis diagnosed

2021 STI Treatment Guidelines: Syphilis
Table 5. Treatment of Syphilis Among Persons with HIV

Note: procaine penicillin G is no longer available in the United States and therefore is not included in this table.

Recommended **Regimen for Treatment of Primary and Secondary Syphilis**

Benzathine penicillin G

Benzathine penicillin G

Tradename:Bicillin-LA

2.4 million units IM in a single dose

Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis among persons with HIV do not result in enhanced efficacy.

Recommended **Regimen for Treatment of Early Latent Syphilis**

Benzathine penicillin G

Benzathine penicillin G

Tradename:Bicillin-LA

2.4 million units IM in a single dose

Recommended **Regimen for Treatment of Late Latent or Latent Syphilis of Unknown Duration**

Benzathine penicillin G

Benzathine penicillin G

Tradename:Bicillin-LA

7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Recommended **Regimen for Treatment of Neurosyphilis, Ocular Syphilis, and Otic Syphilis**

Aqueous crystalline penicillin G

Aqueous crystalline penicillin G

Tradename:Pfizerpen

18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days

Note: The duration of the recommended regimen for neurosyphilis is shorter than the duration of the regimen used for treatment of latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of neurosyphilis treatment to provide a total duration of therapy comparable to treatment of latent syphilis.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

.[28]

- **Early Syphilis (including primary, secondary, and early latent syphilis)**: Treatment of early syphilis (primary, secondary, and early latent) requires a single intramuscular dose of benzathine penicillin G 2.4 million units.[28,37] Studies have demonstrated that enhancing therapy (e.g., using 3 doses of benzathine penicillin G) for early syphilis does not improve serologic or clinical

responses.[38,39] 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 or when penicillin is not available. 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 syphilis should always receive treatment with penicillin. Pregnant women with a penicillin allergy should 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) requires three injections of benzathine penicillin G 2.4 million units intramuscularly given at weekly intervals. 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 (or if penicillin is not available). As noted above, all pregnant women with syphilis should receive penicillin treatment.
- **Neurosyphilis, Ocular Syphilis, and Otosyphilis**: The recommended treatment for neurosyphilis, ocular syphilis, and otosyphilis consists of aqueous crystalline penicillin G 18 to 24 million units per day (administered as 3 to 4 million units intravenously every 4 hours or via continuous infusion) for 10 to 14 days. To provide a similar total duration of neurosyphilis treatment regimen as with late latent syphilis without neurologic involvement, some experts also give intramuscular benzathine penicillin G 2.4 million units once weekly for 1 to 3 weeks after completing the 10 to 14 day treatment regimen. Treatment of neurosyphilis, ocular syphilis, or otosyphilis with agents other than penicillin is not optimal, but limited data suggest ceftriaxone 1-2 g intravenously or intramuscularly daily for 10 to 14 days may be an option in some penicillin-allergic individuals, depending on their penicillin allergy. For pregnant women with neurosyphilis and a penicillin allergy, ceftriaxone should not be used; in such cases, penicillin desensitization is indicated.

Post-Treatment Follow-Up

Persons with HIV who receive treatment for syphilis should have close follow-up to monitor signs, symptoms, and serologic changes in nontreponemal titers (VDRL or RPR) that indicate possible treatment failure or reinfection. The serologic changes in nontreponemal titers are described as a quantitative fold increase or decrease, based on the comparison of baseline and follow-up nontreponemal titers.[28] Most persons with syphilis will have reactive treponemal tests for the remainder of their lives, regardless of treatment or disease activity. Thus, treponemal tests should not be used to assess treatment response and usually are not helpful for future evaluation. The following summarizes recommendations for follow-up clinical and nontreponemal serologic monitoring after treatment of syphilis in people with HIV.[28]

- **Recommended Monitoring**: After treatment for primary or secondary syphilis, repeat clinical and nontreponemal serologic testing at 3, 6, 9, 12, and 24 months should be performed. After treatment for latent syphilis (early or late) without neurologic involvement, follow-up nontreponemal testing should be performed at 6, 12, 18, and 24 months. Individuals who have good clinical and serologic responses after syphilis treatment do not need follow-up CSF examinations, even if they were initially diagnosed with neurosyphilis.
- **Adequate Serologic Response**: Individuals with HIV who achieve at least a 4-fold decline in nontreponemal titers within 24 months after treatment are considered to have achieved an adequate serologic response, which is sometimes referred to as serologic cure or serologic response.
- **Lack of Seroreversion**: In some instances, individuals achieve a 4-fold or greater decline in nontreponemal titers within 24 months after treatment, but they have persistently reactive nontreponemal titers. This situation is usually referred to as lack of seroreversion or serofast. There is no evidence that providing additional antibiotics changes outcomes in this situation. Therefore, in the absence of clinical manifestations that suggest treatment failure or new syphilis infection, additional antibiotic treatment for syphilis is not recommended in this setting.
- **Inadequate Serologic Response**: For individuals who fail to achieve at least a post-treatment 4-fold decline in nontreponemal titers within 24 months, the optimal management is unknown. The evaluation of these individuals should include, at a minimum, a neurologic examination and annual clinical follow-up that includes repeated syphilis serologic studies. Syphilis retreatment is

recommended when follow-up cannot be ensured or if the person initially had a high titer (greater than 1:32) that did not decrease at least 4-fold in the 24-month post-treatment period.
    - If neurologic manifestations are present, then evaluation with lumbar puncture and CSF is indicated, with treatment guided by the CSF results.
    - If no neurologic manifestations are present, then the recommended retreatment regimen should consist of weekly intramuscular injections of benzathine penicillin G 2.4 million units for 3 weeks.
- **Probable Reinfection or Treatment Failure**: Reinfection or treatment failure is likely if any of the following occur: (1) syphilis-related signs or symptoms persist or recur, (2) the person experiences new signs or symptoms attributable to primary or secondary syphilis, or (3) repeated serologic testing shows a 4-fold (or greater) increase in nontreponemal titer that persists for longer than 2 weeks. If reinfection or treatment failure is likely, evaluation for neurosyphilis with lumbar puncture and CSF evaluation is recommended if (1) new neurologic manifestations are present or (2) the individual has not had any recent sexual exposures (in the prior 6 months in persons treated for primary or secondary syphilis and the prior 12 months for persons treated for latent and other stages of syphilis). For persons who undergo lumbar puncture with CSF evaluation, the treatment is then guided based on the CSF results.
    - If the CSF tests suggest neurosyphilis, treat for neurosyphilis.
    - If neurosyphilis has been ruled out (clinically or with CSF results), then retreat based on the syphilis stage at the prior syphilis diagnosis.

Genital Herpes

Infections with herpes simplex virus (HSV) frequently occur 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.[40,41] 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.[42,43,44,45] Persons with HIV, when compared to persons without HIV, tend to have more severe HSV lesions and more asymptomatic shedding of HSV-2 in the genital tract.[43] Furthermore, HSV-2 reactivation, including asymptomatic shedding without clinically apparent lesions, has been shown to increase the rates of HIV transcription, resulting in increased HIV RNA levels in both plasma and genital tissues, but these changes are negligible in persons on potent antiretroviral therapy.[46,47,48]

Clinical Manifestations

Infection with HSV-1 most often manifests with lesions of the mouth and/or lips, whereas HSV-2 more commonly causes genital lesions. Nevertheless, 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.[41] Ulcers caused by HSV tend to be painful, erythematous, and have “punched out” borders; genital HSV lesions may be present on the penis, scrotum, vulva, perianal region, and gluteal cleft (Figure 6). If untreated, most persons have symptoms that persist for 5 to 10 days; anti-herpes therapy initiated at the 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.[41,49,50] In addition, persons who have just started effective antiretroviral therapy may develop unusual ulcerative lesions as a manifestation of immune reconstitution syndrome.[43]

Laboratory Diagnosis

The diagnosis of HSV can be difficult on a clinical basis alone, and lesions can mimic other infections. The diagnosis of genital herpes, therefore, should be pursued through laboratory testing.[51] The NAAT (e.g., HSV DNA PCR), is the most sensitive method and preferred test for establishing the diagnosis of HSV;[51,52,53] viral culture and antigen detection are also an option, though less preferable.[17,54] When obtaining clinical samples, the base of the lesion should be scraped to ensure an adequate number of cells are obtained. Serologic tests are available using HSV type-specific IgG assays that are based on antigens specific to HSV-1 (gG1) and HSV-2 (gG2); these tests can reliably distinguish antibodies to HSV-2 from antibodies to HSV-1.[51] Type-specific IgG serologic testing, if performed, should utilize a two-step process with an initial screening test and a confirmatory second test (for samples positive on the initial test).[51]

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 baseline serologic testing for persons with HIV who have any of the following: (1) a history of genital ulcer disease for which the cause has not been identified, (2) atypical genital lesions that were not confirmed as HSV by PCR or culture, and/or (3) a sex partner with genital HSV.[41,51,55]

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 for episodic genital herpes in persons with HIV is a 5-to 10-day course of acyclovir, valacyclovir, or famciclovir.[41,51] Intravenous acyclovir may rarely be required for severe mucocutaneous disease.[41,51]

2021 STI Treatment Guidelines: Genital Herpes
Table 6. Episodic Therapy for Recurrent Genital Herpes Among Persons with HIV*

Recommended **Regimens**

Acyclovir

Acyclovir

Tradename:Zovirax

400 mg orally three times a day for 5–10 days

Recommended **Regimens**

Famciclovir

Famciclovir

Tradename:Famvir

500 mg orally twice a day for 5–10 days

Recommended **Regimens**

Valacyclovir

Valacyclovir

Tradename:Valtrex

1 g orally twice a day for 5–10 days

*For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

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 the use of suppressive therapy should be made without regard to the individual's CD4 cell count or changes in CD4 cell count. Daily suppressive valacyclovir has been shown to reduce HSV-2 transmission in heterosexual HSV-serodifferent couples without HIV, but similar findings were not observed when using twice-daily acyclovir suppressive therapy in persons with HIV.[56,57] The recommended daily suppressive therapy options for people with HIV include acyclovir, valacyclovir, and famciclovir.[51]

2021 STI Treatment Guidelines: Genital Herpes
Table 7. Daily Suppressive Therapy Among Persons with HIV

Recommended **Regimens**

Acyclovir

Acyclovir

Tradename:Zovirax

400–800 mg orally two to three times a day

Recommended **Regimens**

Famciclovir

Famciclovir

Tradename:Famvir

500 mg orally twice a day

Recommended **Regimens**

Valacyclovir

Valacyclovir

Tradename:Valtrex

500 mg orally twice a day

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Acyclovir-Resistant HSV

Reports have documented rates of resistance to acyclovir in up to 5% of persons with HIV and HSV coinfection,[49] 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 7).[58,59,60] 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.

Treatment of Acyclovir-Resistant HSV

The most common mechanism of acyclovir resistance is absent or decreased production by HSV of the enzyme thymidine kinase, an enzyme required for the initial step in the triphosphorylation of acyclovir.[60] The preferred treatment for acyclovir-resistant HSV is intravenous foscarnet, but this medication can cause significant adverse effects, including renal and electrolyte abnormalities.[41,58,61] 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.[41] (Table 8)

Human Papillomavirus and Anogenital Warts

Anogenital warts, also called condyloma acuminata, are the most common viral STI and are caused by various strains of human papillomavirus (HPV), which is a small double-stranded DNA virus. More than 100 types of 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. Most sexually active adults will acquire HPV infection at some point in their lives, and in most cases, the virus is cleared spontaneously. Men and women with HIV have increased prevalence, greater severity, and higher persistence of HPV infection.[62,63] 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.[64,65] Among men with HIV who have sex with men, younger age and lower HIV RNA levels have been associated with higher rates of HPV clearance.[66]

Clinical Manifestations

Typical condyloma acuminata are flesh-colored and can range from smooth, flattened lesions to verrucous papules (Figure 8).[65] 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 detects 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).[64,65] 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.[64,65,67] For a full discussion of cervical cancer screening in women and anal cancer screening in men with HIV, 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.[65] 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. For diagnosing genital warts, the routine use of HPV DNA testing or clinical application of 3 to 5% acetic acid onto affected areas is not recommended.[68]

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 sex partners, and there is no evidence that the presence of genital warts (or their treatment) has any effect on cervical cancer risk in women.[68] Compared to persons without HIV, those with HIV have more treatment-refractory warts and recurrence rates are high, especially in the first three months after treatment.[65] Treatment options can be categorized into patient-applied or provider-applied modalities, and they include chemical or physical destruction, immunologic therapy, and surgical therapy.[68] The recommendations for treatment of anogenital warts are the same for persons with or without HIV.[68]

- Patient-applied options include imiquimod 3.75% cream, imiquimod 5% cream, podofilox 0.5%

solution or gel, 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.
- 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.[68]

Prevention

The 9-valent human papillomavirus (9vHPV) 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).[69] 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.[65,69,70] The HPV vaccine is not routinely recommended for persons with HIV who are 27 to 45 years of age or older, but can be considered with shared decision-making.[65,71] For additional details on recommendations for the use of the HPV vaccine in persons with HIV, see the Human Papillomavirus Vaccine section in the topic review on Immunizations in Module 2.

Trichomoniasis

Trichomoniasis is the most common nonviral STI 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%.[72] 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.[34,73,74]

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.[72,75,76] 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 at least annually thereafter.[72,77] Currently, there are no guidelines that recommend screening men for infection with *T. vaginalis*.

Laboratory Diagnosis

Multiple sensitive and specific NAAT assays for the detection of *T. vaginalis* are commercially available and FDA-cleared for use in women, including testing on vaginal, endocervical, or urine specimens. 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 with these methods than with NAAT.[78] For men, NAAT for *T. vaginalis* can be used for urethral swabs and urine samples (as long as validated per Clinical Laboratory Improvement Amendments [CLIA] regulations), but one study showed much higher sensitivity with urethral (penile-meatal) swabs.[79] Use of a 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 recommended treatment for trichomoniasis in women with HIV is metronidazole 500 mg orally twice daily for 7 days.[34,72] This recommendation is based on a randomized controlled trial of women with trichomoniasis and HIV that found single-dose therapy with metronidazole 2 g was less effective than a 7-day metronidazole course.[80] Alternative regimens should not be used to treat trichomoniasis in women with HIV.[72]
- **Treatment of Trichomoniasis in Men**: The 2021 STI Treatment Guidelines do not provide specific recommendations for the treatment of trichomoniasis for men with HIV.[72] The recommended treatment of trichomoniasis in men without HIV is oral metronidazole 2 g in a single dose, and the alternative is tinidazole 2 g in a single dose.[72] Rescreening 3 months after treatment for trichomoniasis is not recommended for men.[72,77]
- **Management of Sex Partners**: Any current sex partners of individuals diagnosed with trichomoniasis should be referred for presumptive treatment. Furthermore, all individuals who are diagnosed or being treated for trichomoniasis should be counseled to abstain from sexual activity until they and their partners have completed a course of treatment and all have symptom resolution.[72]
- **Follow Up**: Due to significant risk of reinfection, sexually active women should be retested 3 months after treatment for trichomoniasis, regardless of whether their sex partners have also been treated.[72]

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 sex partners.[81]

- **Recommended Treatment**: The recommended empiric treatment of cervicitis consists of doxycycline 100 mg orally twice daily for 7 days. Concurrent treatment for gonococcal infection with a single dose of intramuscular ceftriaxone 500 mg should be provided if (1) the person is at risk for gonorrhea (age younger than 25 years, a new sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) or lives in a community where the prevalence of gonorrhea is high, (2) follow-up cannot be ensured, or (3) testing with a NAAT for gonorrhea is not done.[81] Pregnant women should receive azithromycin 1 g orally as a single dose as an alternative to doxycycline. 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.[81,82] Repeating initial therapy, or treating with a longer course of standard therapy has not been established to improve response rates in persistent cervicitis.

Urethritis

Urethritis is characterized by dysuria, urethral pruritus, and urethral discharge (mucoid, mucopurulent, or purulent).[81] For individuals with symptoms compatible with urethritis, any one of the following criteria is sufficient to make a diagnosis of urethritis: (1) mucopurulent discharge, (2) Gram's stain of a urethral smear sample that shows 2 or more leukocytes per high-power field (oil immersion) microscopy, or (3) a first-void urine sample that is positive for leukocyte esterase test or has 10 or more leukocytes per high-power field on microscopic examination of the urine sediment.[81,83] All persons with urethritis should have a NAAT for *N. gonorrhoeae* and *C. trachomatis*. Gonococcal urethritis can be diagnosed if the Gram's stain of a urethral smear reveals leukocytes with gram-negative intracellular diplococci. Urethritis without evidence of gram-negative intracellular diplococci is referred to as nongonococcal urethritis (NGU).

- **Recommended Treatment**: Empiric treatment for urethritis should have efficacy against both gonorrhea and chlamydia; the preferred regimen is ceftriaxone 500 mg as a single intramuscular dose plus doxycycline 100 mg orally twice daily for 7 days.[81] If gonorrhea is deemed unlikely based on a negative point-of-care test (no evidence of intracellular diplococci on Gram's stain, methylene blue, or gentian violet stain), then initial therapy with doxycycline alone is recommended. The alternative to doxycycline is azithromycin 1 g orally in a single dose or azithromycin 500 mg on day 1, followed by 250 mg daily for 4 days.

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 years are at increased risk for non-sexually transmitted epididymitis that is 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 epididymitis, including cytomegalovirus, *Salmonella*, *Toxoplasma gondii*, *Ureaplasma urealyticum*, *Corynebacterium* sp., *Mycobacterium* sp., and *Mima polymorpha*, fungal infections, and mycobacteria.[84]

- **Recommended Treatment**: The treatment for acute epididymitis is stratified based on three likely scenarios: (1) acute epididymitis most likely caused by chlamydia or gonorrhea, (2) acute epididymitis most likely caused by chlamydia, gonorrhea, or enteric organisms (men who practice insertive anal sex), or (3) acute epididymitis most likely caused by enteric organisms only.[84] In persons at risk for enteric organisms, levofloxacin should be given in addition to the doxycycline and ceftriaxone used for the treatment of *C. trachomatis* and *N. gonorrhoeae*.[84,85,86]

The most common infectious etiologies of proctitis are *C. trachomatis* (including subtypes that cause LGV), *N. gonorrhoeae, T. pallidum*, and herpes simplex virus.[87] Diagnosis should be made by visual inspection (via anoscopy or sigmoidoscopy), Gram's staining of a smear of anorectal exudate or secretions, stool examination, and culture.

- **Recommended Treatment**: For persons with anorectal exudate identified by clinical examination or by detection of polymorphonuclear leukocytes on a Gram's stain smear of anorectal secretions, presumptive therapy for proctitis should be administered.[87] The recommended initial empiric therapy for acute proctitis should include treatment for *C. trachomatis* and *N. gonorrhoeae* with ceftriaxone 500 mg in a single intramuscular dose plus doxycycline 100 mg orally twice a day for 7 days.[87] Note that for persons who have symptoms consistent with LGV (bloody rectal discharge, perianal or mucosal ulcers, or tenesmus) in conjunction with a positive rectal chlamydia test, the duration of doxycycline therapy should be extended to 21 days to treat LGV.[87] In addition, the initial empiric treatment should also include an oral antiviral (acyclovir, famciclovir, or valacyclovir) to treat genital herpes if painful perianal ulcers are present or mucosal ulcers are detected on anoscopy.[87] The treatment regimen should be expanded or modified based on testing results.

Summary Points

- 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 regimen for gonococcal infections is a single dose of intramuscular ceftriaxone 500 mg (in persons less than 150 kg), with or without oral doxycycline 100 mg twice daily for 7 days, depending on whether chlamydia infection has been ruled out. Pregnant women should receive a single 1 g oral dose of azithromycin instead of doxycycline.
- The recommended treatment for chlamydia in nonpregnant adults with HIV is doxycycline 100 mg orally twice daily for 7 days; during pregnancy, azithromycin 1 g orally in a single dose is recommended.
- Lymphogranuloma venereum, an infection caused by *C*. *trachomatis* serovars L1, L2, and L3, is characterized by painful inguinal adenopathy or proctitis. The recommended treatment of LGV in nonpregnant persons with HIV is doxycycline 100 mg orally twice daily for 21 days.
- Treatment for syphilis depends on the stage of infection and whether neurosyphilis is suspected or documented. Individuals with HIV who are treated for syphilis require serologic follow-up for at least 24 months after completion of therapy.
- For treatment of trichomoniasis in women with HIV, a 7-day course of oral metronidazole 500 mg twice daily is recommended, whereas in men, a single 2-g dose of metronidazole is recommended.
- 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 persons without HIV; suppressive therapy with valacyclovir, acyclovir, or famciclovir, 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.

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Figures

Figure 1 Gonorrhea: Number of Reported Cases by Age Group, United States, 2023

Source: Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023. Atlanta: US Department of Health and Human Services. 1-329.

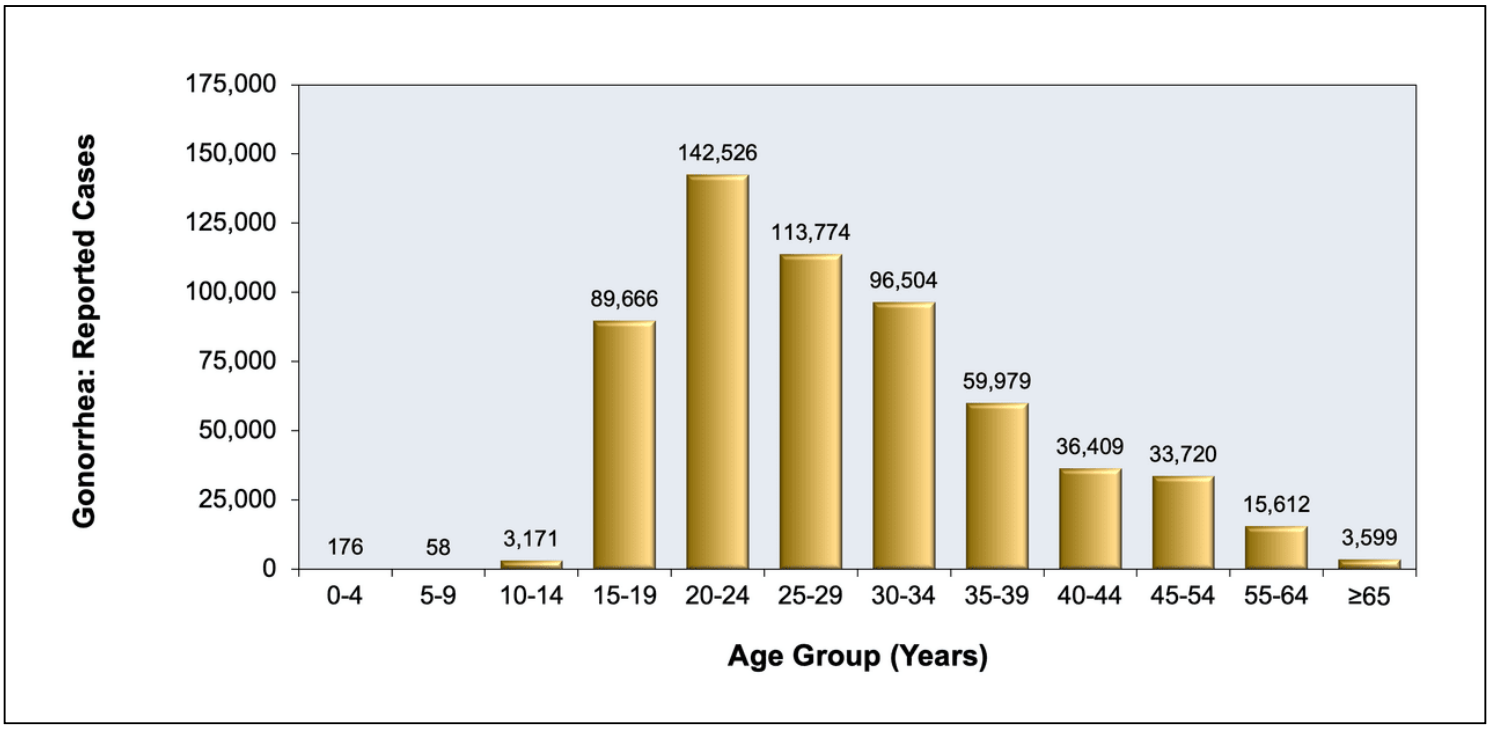

Figure 2 Chlamydia: Number of Reported Cases by Sex and Age Group, United States, 2023

Source: Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023. Atlanta: US Department of Health and Human Services. 1-329.

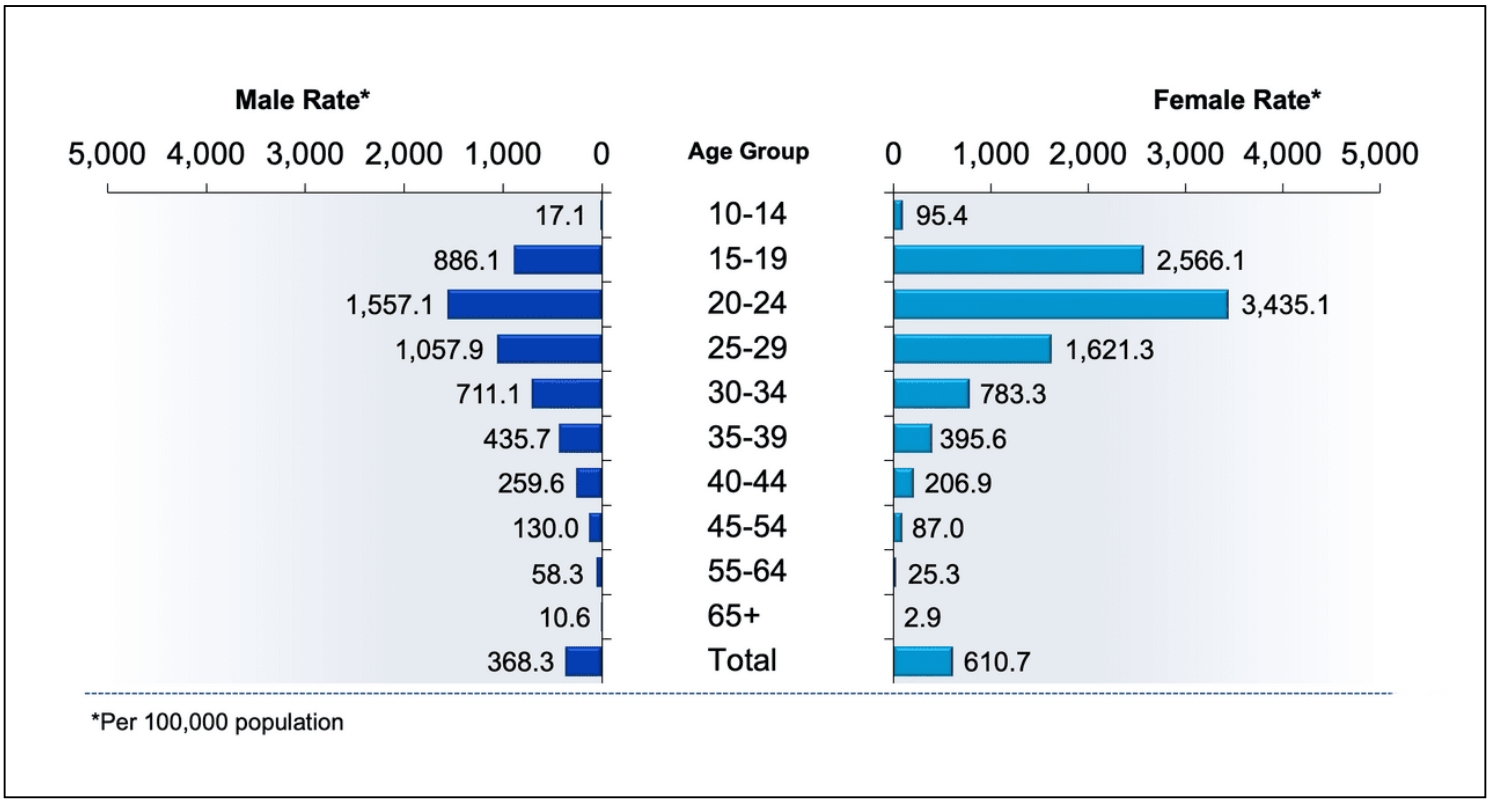

Figure 3 Syphilis: Number of Cases with All Stages of Infection, United States, 2000-2023

Source: Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023. Atlanta: US Department of Health and Human Services. 1-329.

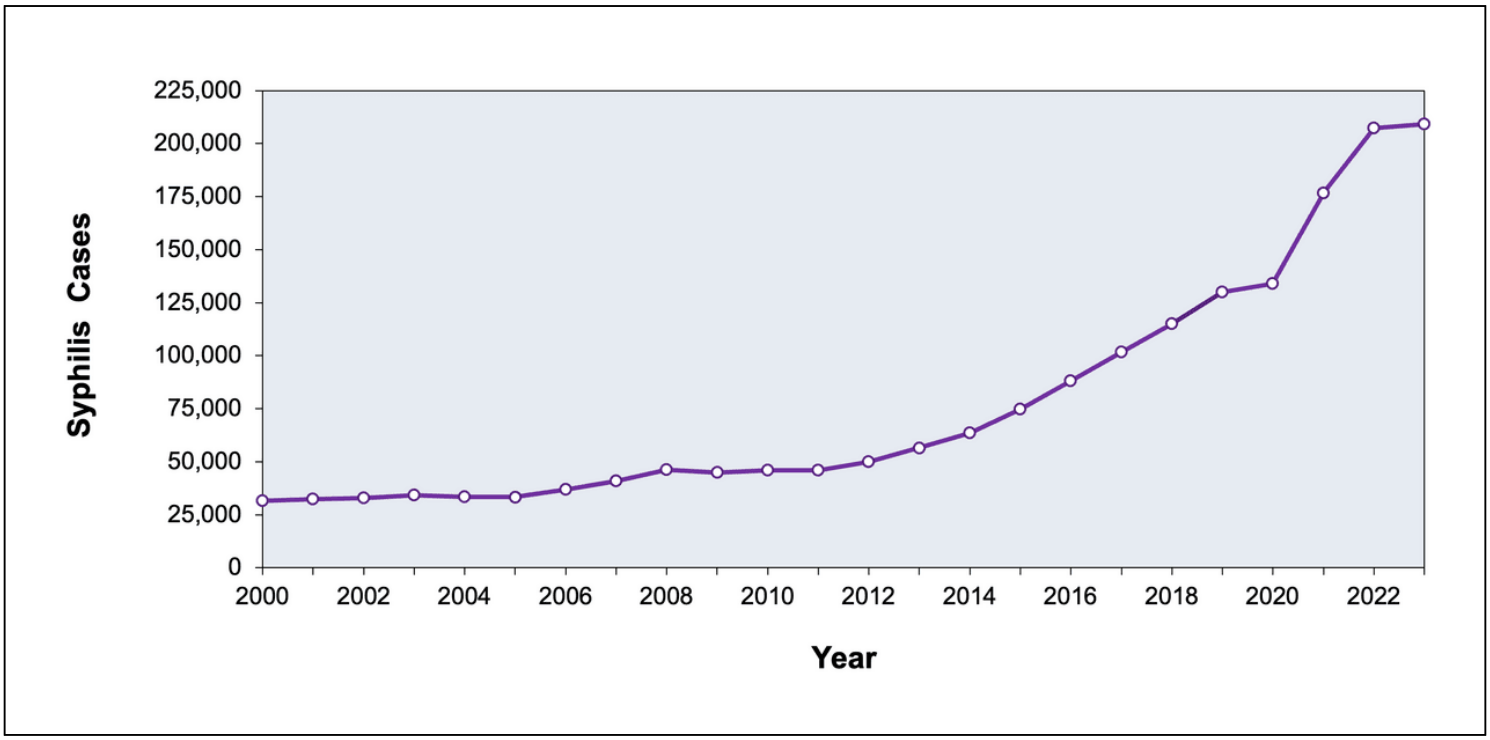

Figure 4 (Image Series) - Secondary Syphilis (Image Series) - Figure 4 (Image Series) - Secondary Syphilis
Image 4A: Diffuse Erythematous Maculopapular Lesions in Man with HIV and Secondary Syphilis

Photograph credit: David H. Spach, MD

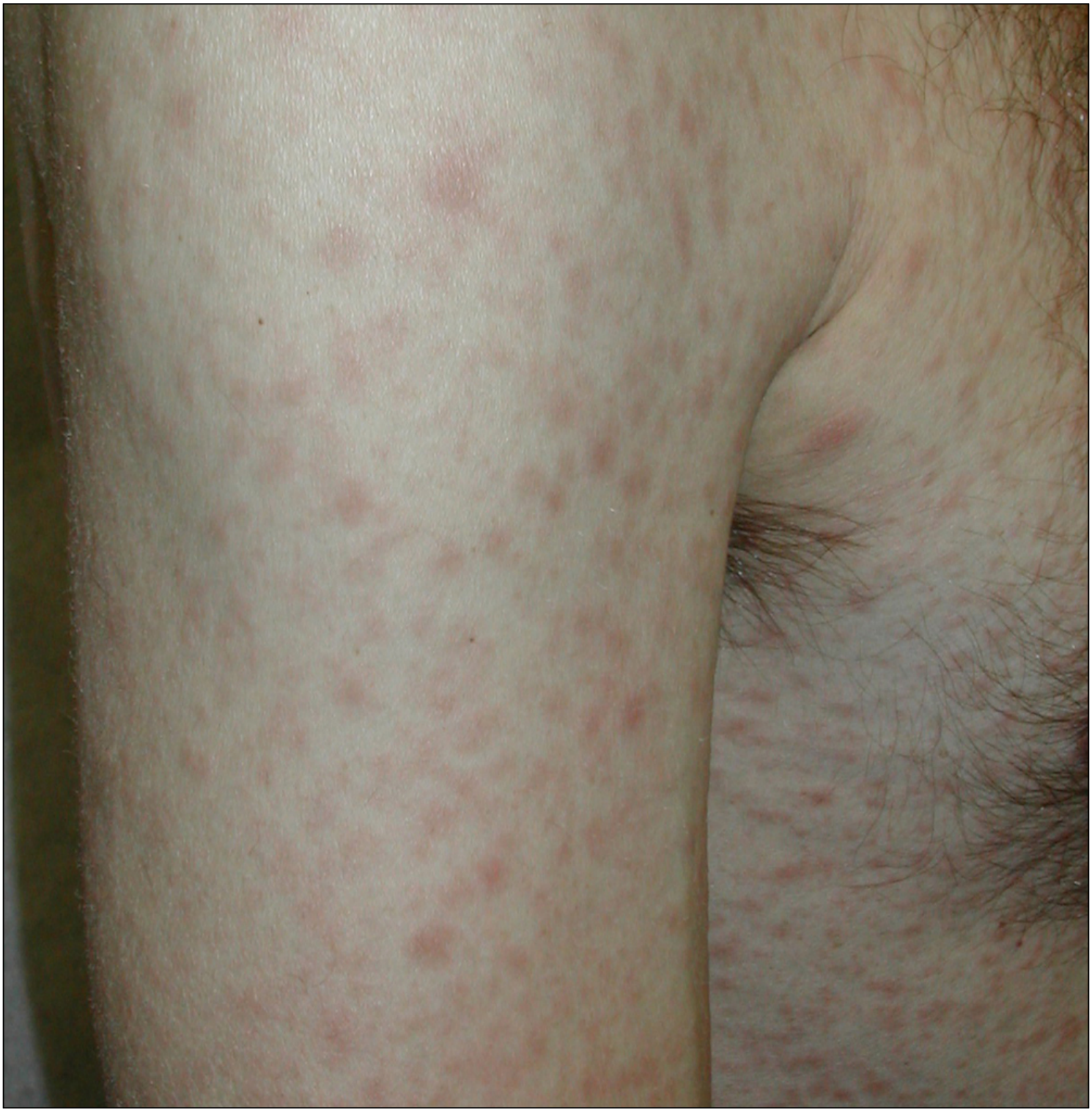

Figure 4 (Image Series) - Secondary Syphilis
Image 4B: Secondary Syphilis: Diffuse Erythematous Maculopapular Lesions

Photograph credit: David H. Spach, MD

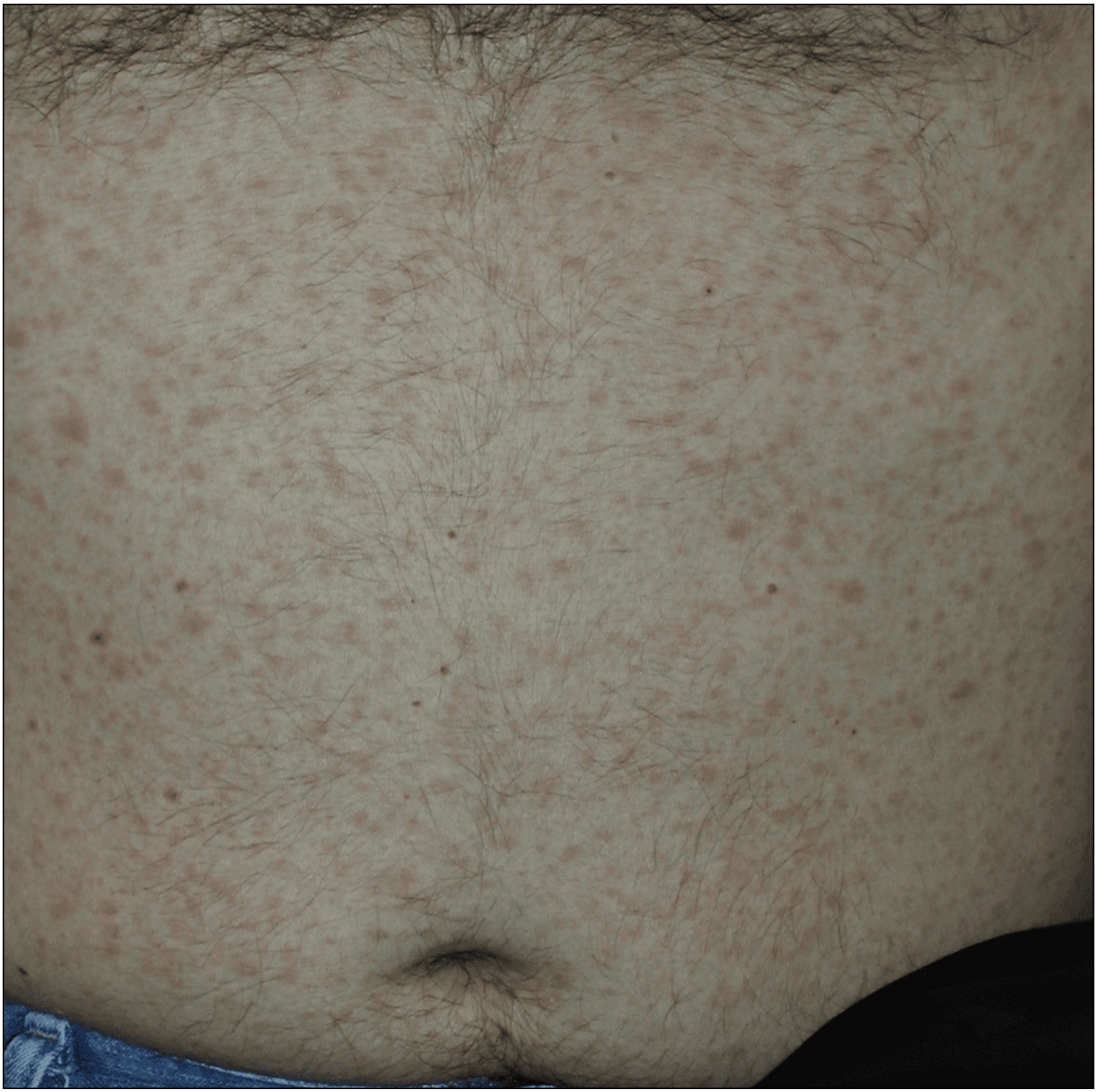

Figure 4 (Image Series) - Secondary Syphilis
Image 4C: Secondary Syphilis: Papular Lesions on Abdomen

Photograph credit: Negusse Ocbamichael, PA

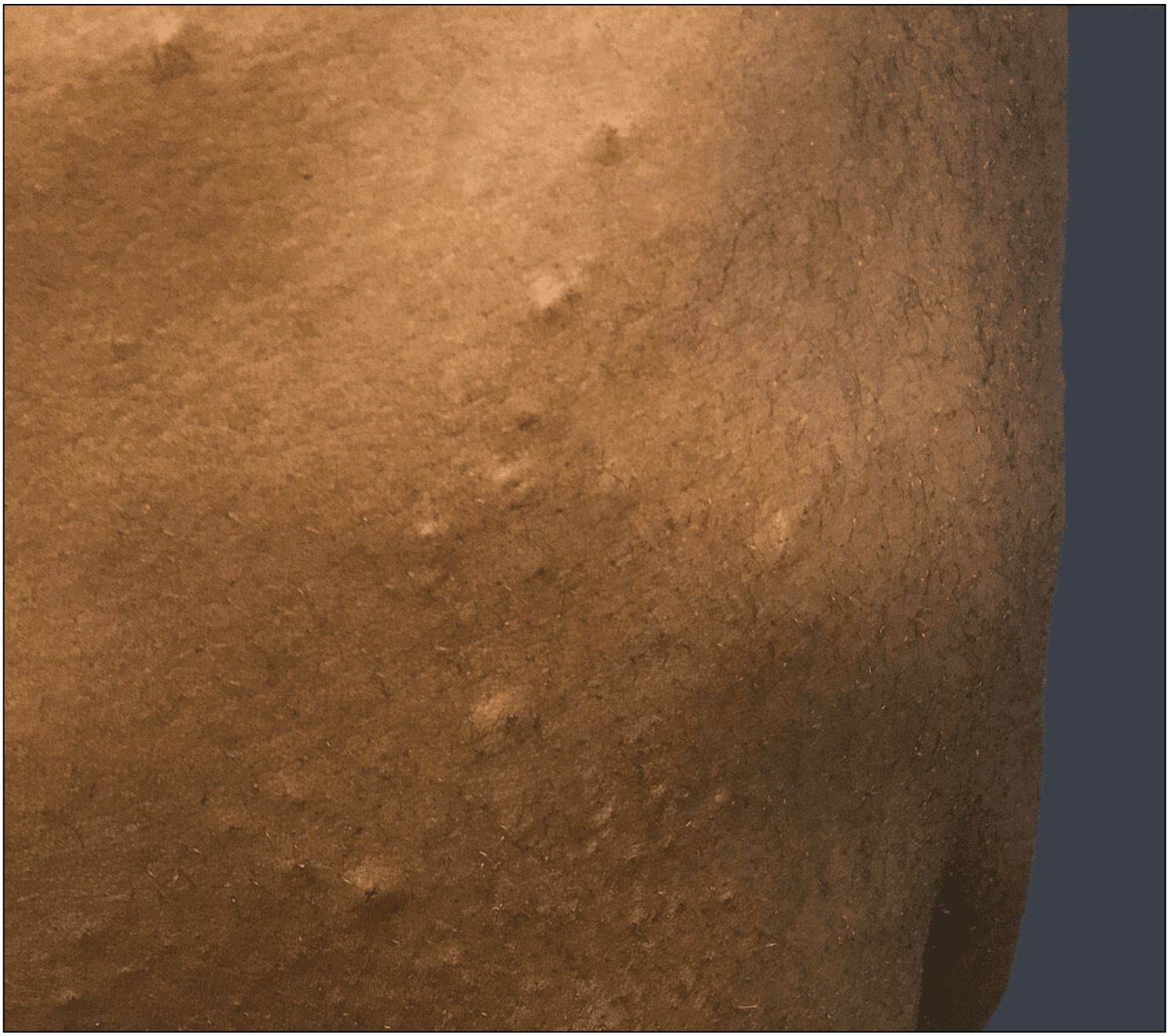

Figure 4 (Image Series) - Secondary Syphilis
Image 4D: Secondary Syphilis: Papular Lesions on Hand

Photograph credit: David H. Spach, MD

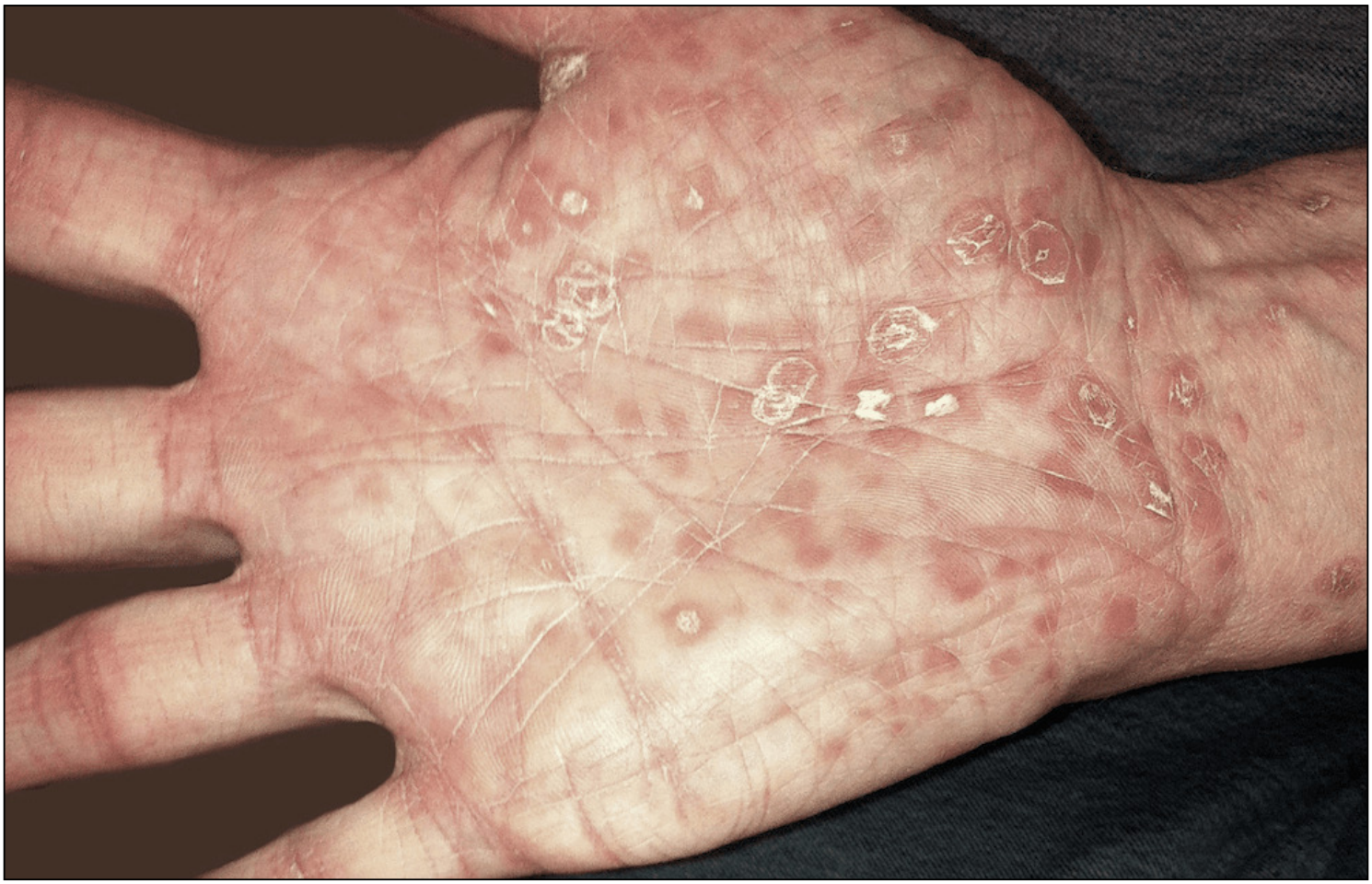

Figure 5 (Image Series) - Syphilis Serologic Screening Algorithms (Image Series) - Figure 5 (Image Series) - Syphilis Serologic Screening Algorithms
Image 5A: Reverse Sequence Algorithm

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.

Source: Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60:133-7.

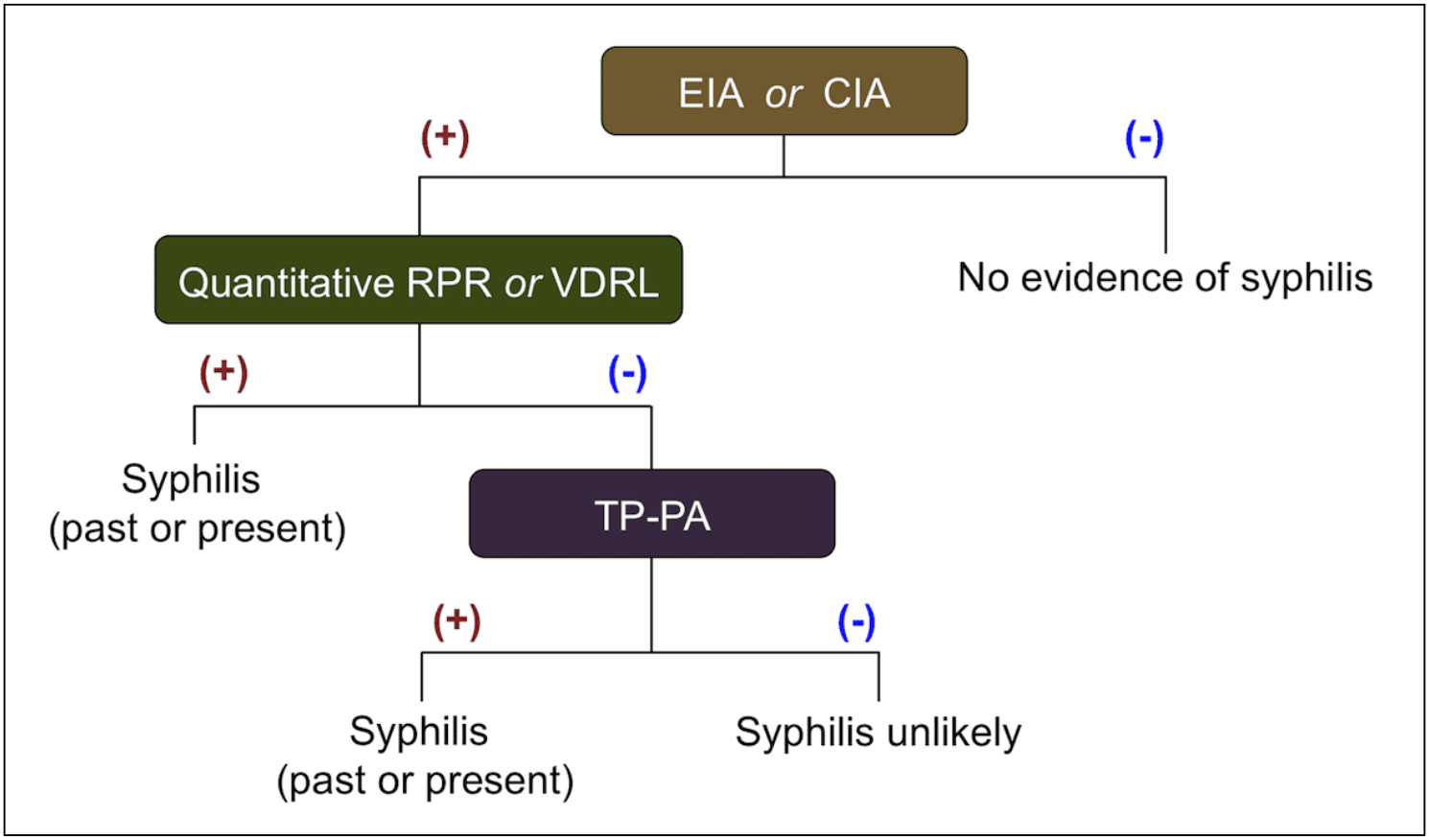

Figure 5 (Image Series) - Syphilis Serologic Screening Algorithms
Image 5B: Traditional Algorithm

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.

Source: Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60:133-7.

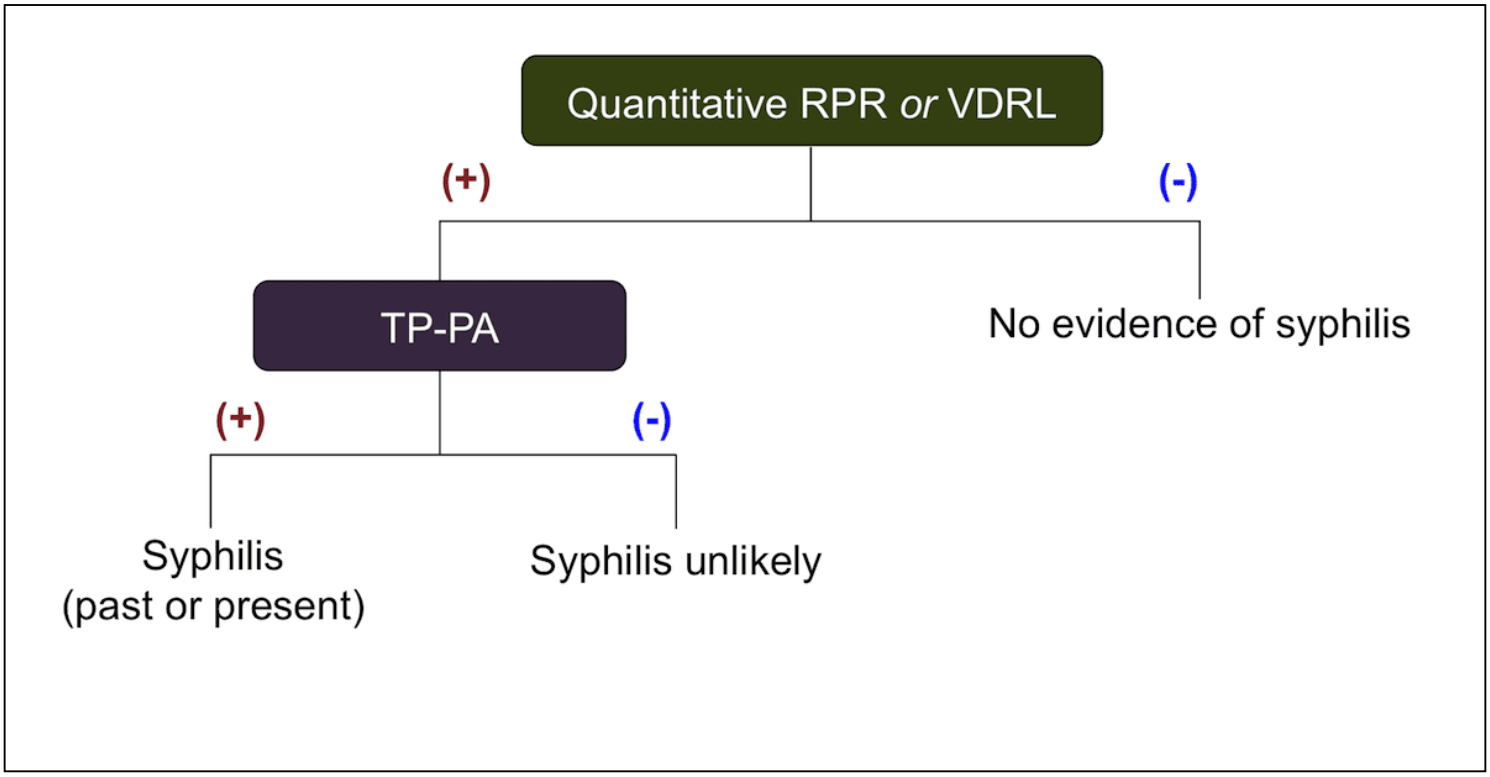

Figure 6 (Image Series) - Genital Herpes Manifestations (Image Series) - Figure 6 (Image Series) - Genital Herpes Manifestations
Image 6A: Multiple Ulcerated Lesions on Penis Caused by Herpes Simplex Infection

Photograph credit: Negusse Ocbamichael, PA

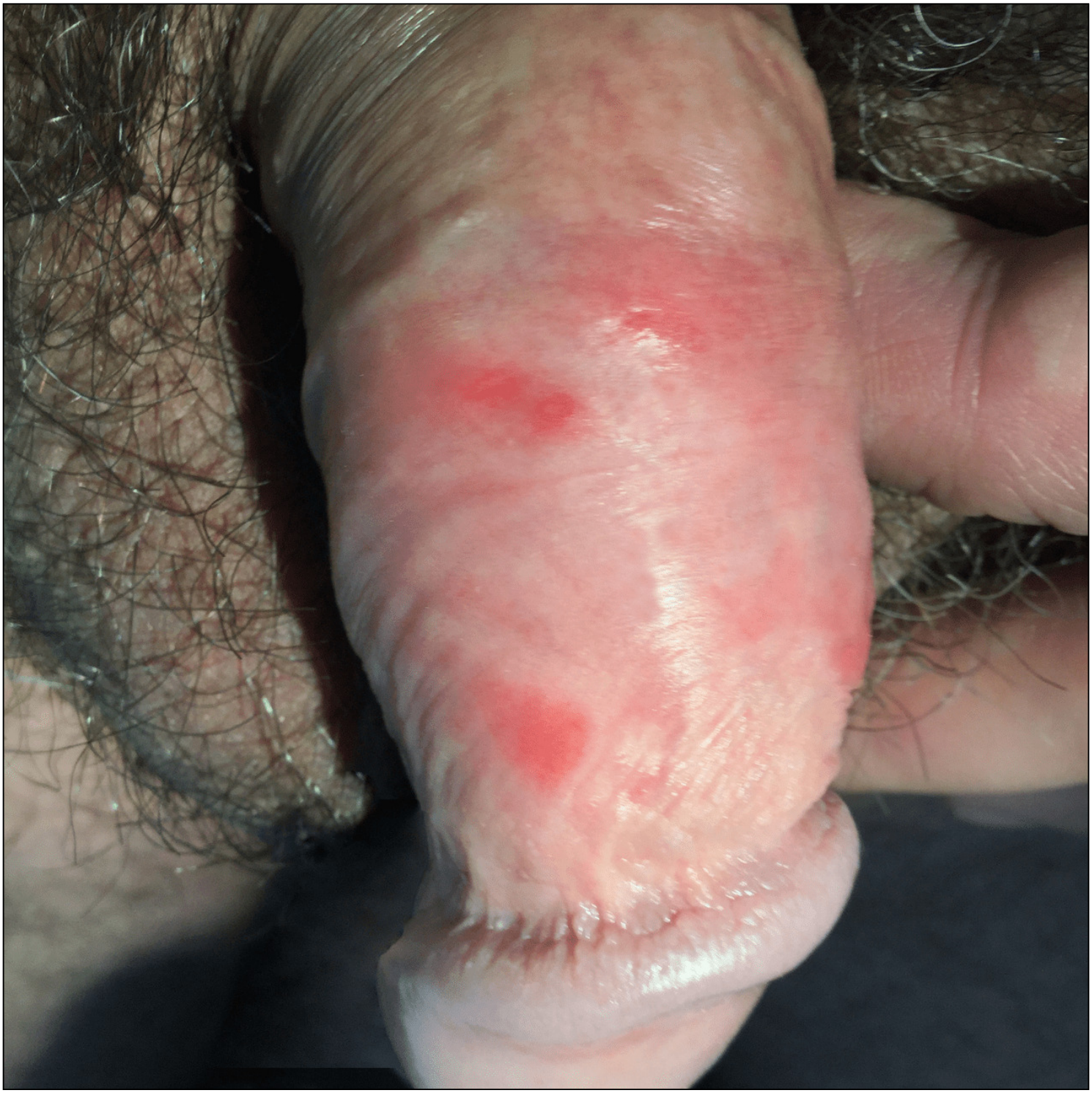

Figure 6 (Image Series) - Genital Herpes Manifestations
Image 6B: Multiple Ulcerated Lesions on the Scrotum of a Man with HIV and CD4 Count Less than 50 cells/mm^3

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 credit: David H. Spach, MD

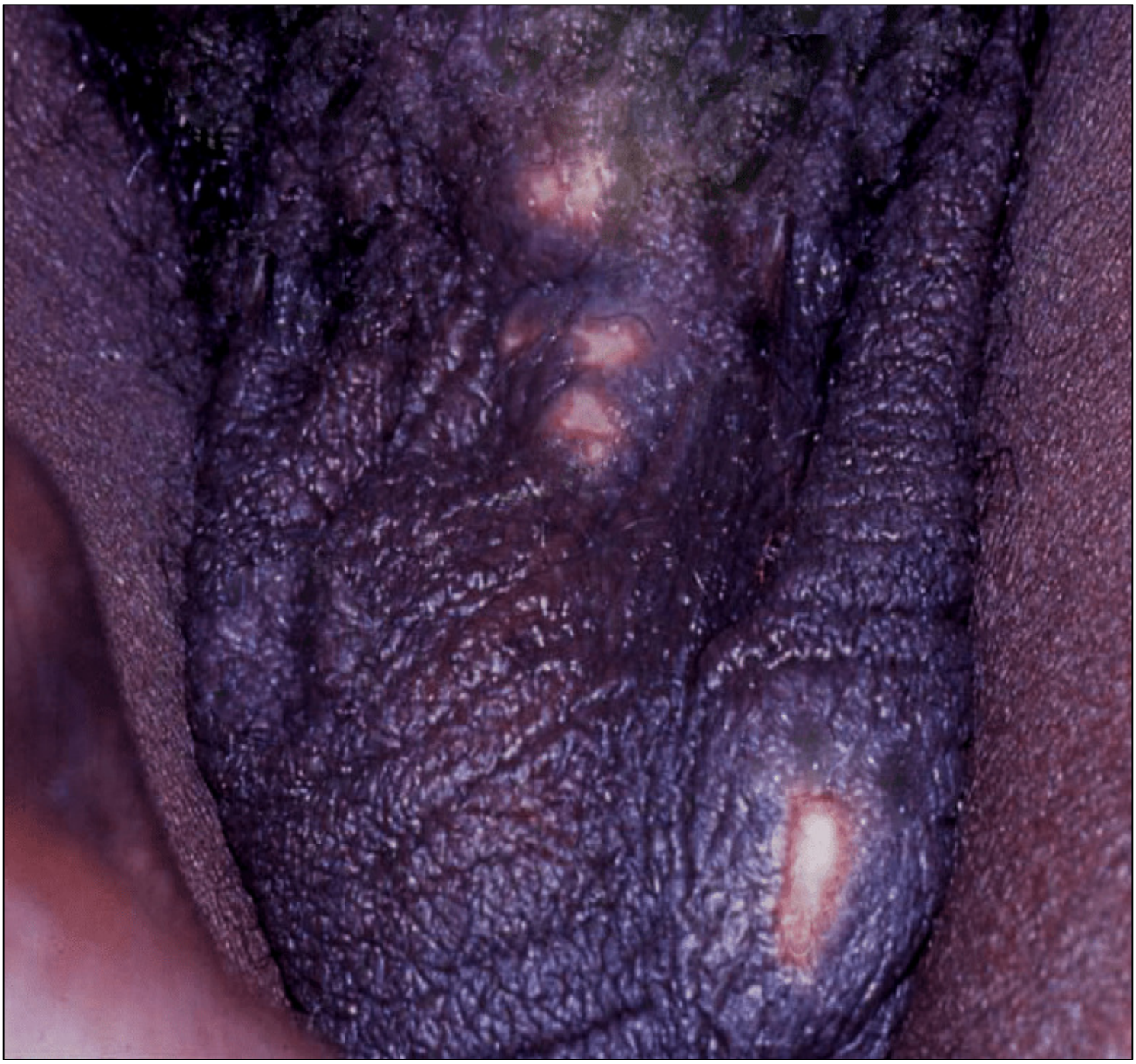

Figure 6 (Image Series) - Genital Herpes Manifestations
Image 6C: HSV Lesion in Gluteal Cleft

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

Photograph credit: David H. Spach, MD

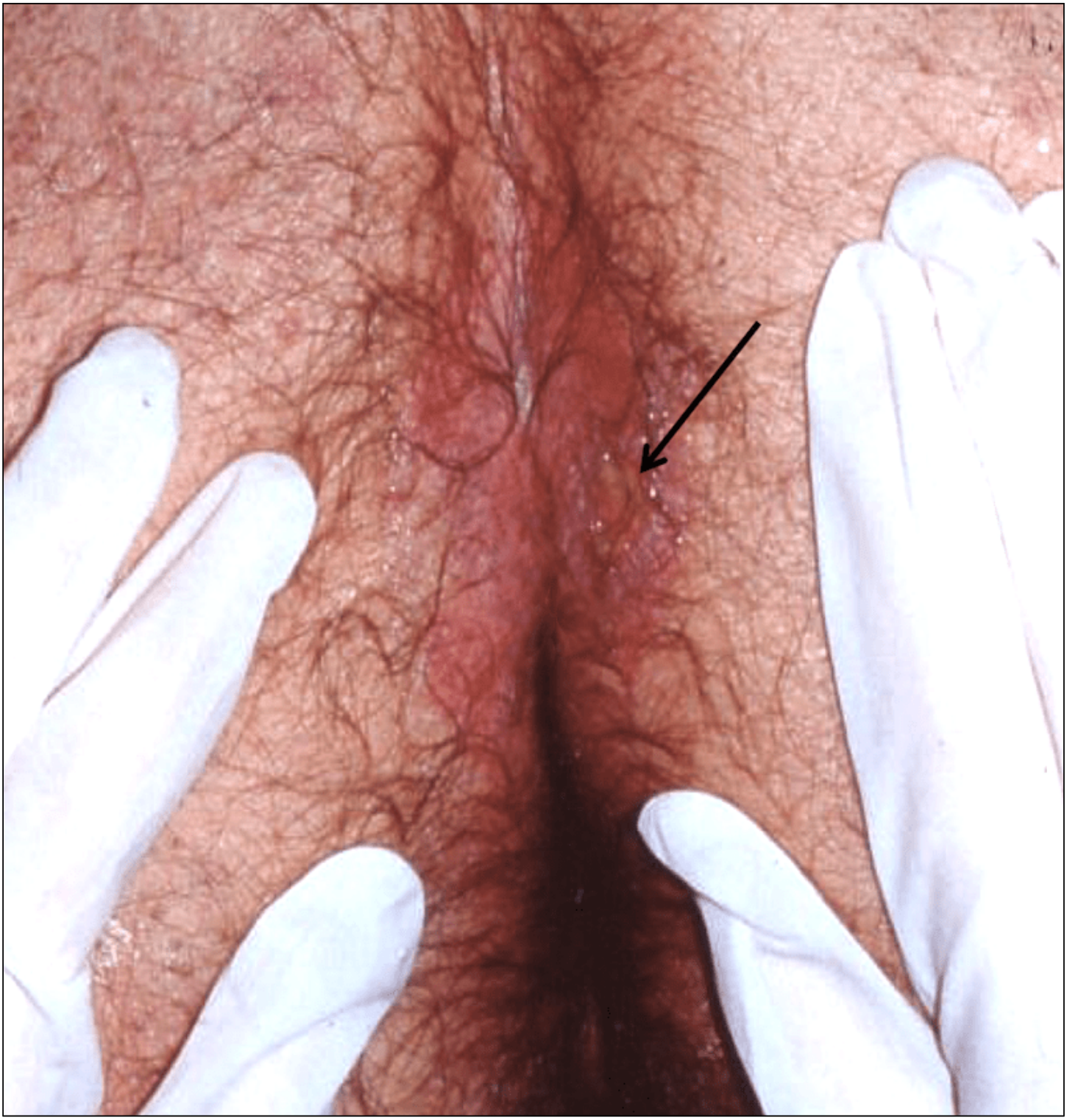

Figure 6 (Image Series) - Genital Herpes Manifestations
Image 6D: Perianal HSV Infection

Multiple painful perianal lesions caused by HSV-2 infection.

Photograph credit: David H. Spach, MD

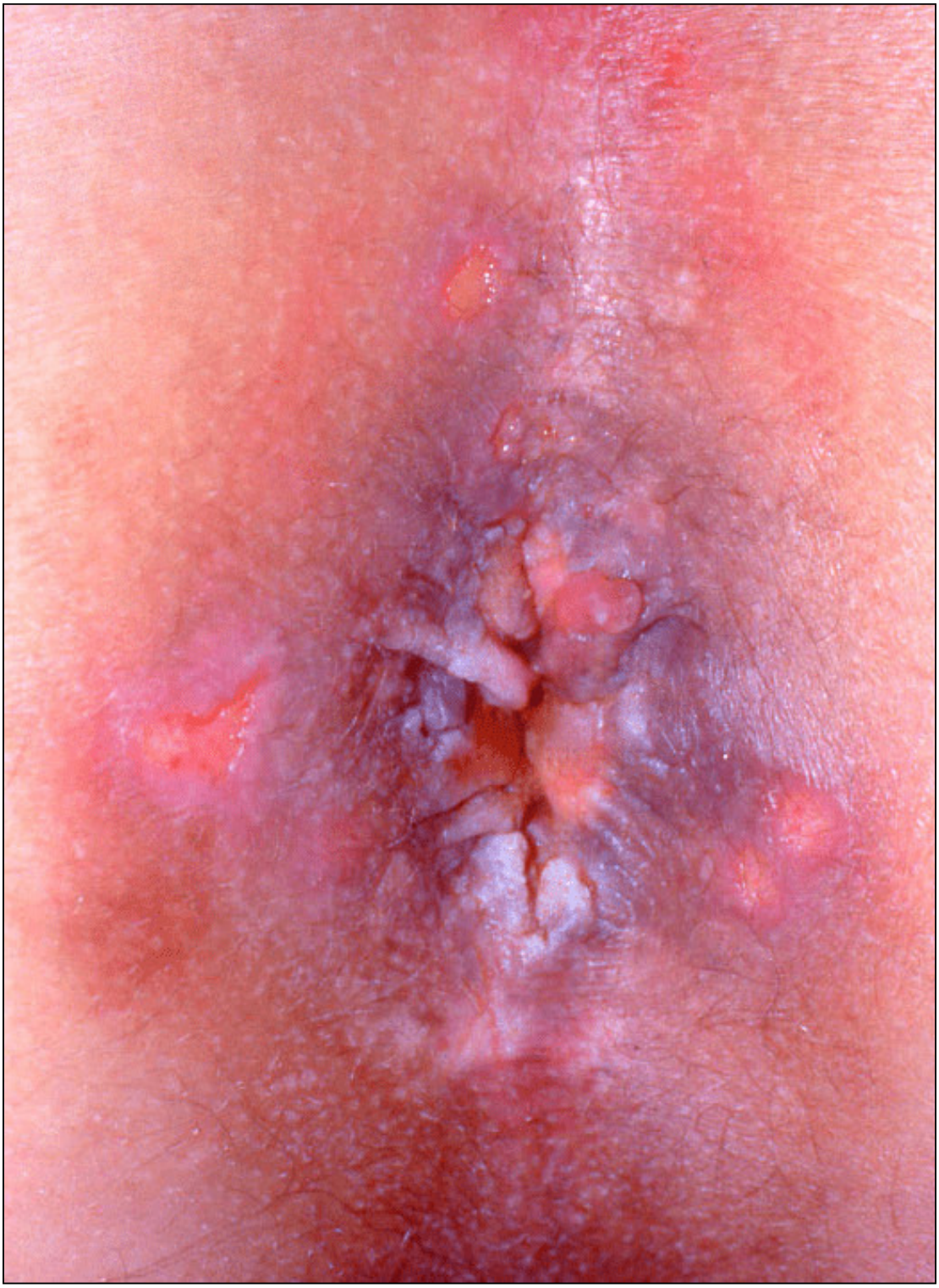

Figure 7 Acyclovir-Resistant HSV Lesion in Gluteal Fold

This man with advanced HIV developed a slowly expanding ulcerating lesion in the upper region of the gluteal cleft.

Photograph credit: David H. Spach, MD

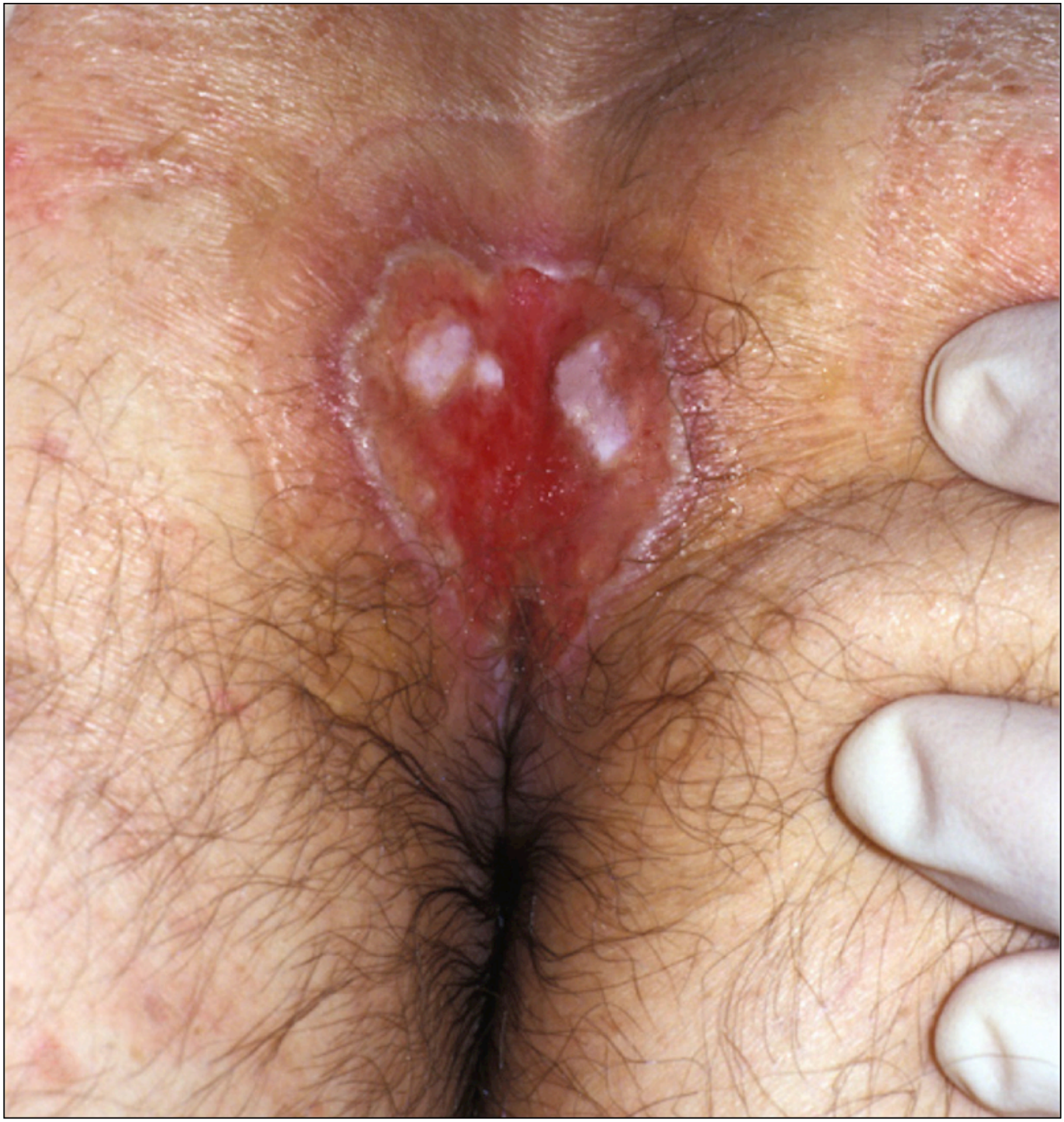

Figure 8 Multiple Warts on Shaft of Penis in Man with HIV

Photograph credit: David H. Spach, MD

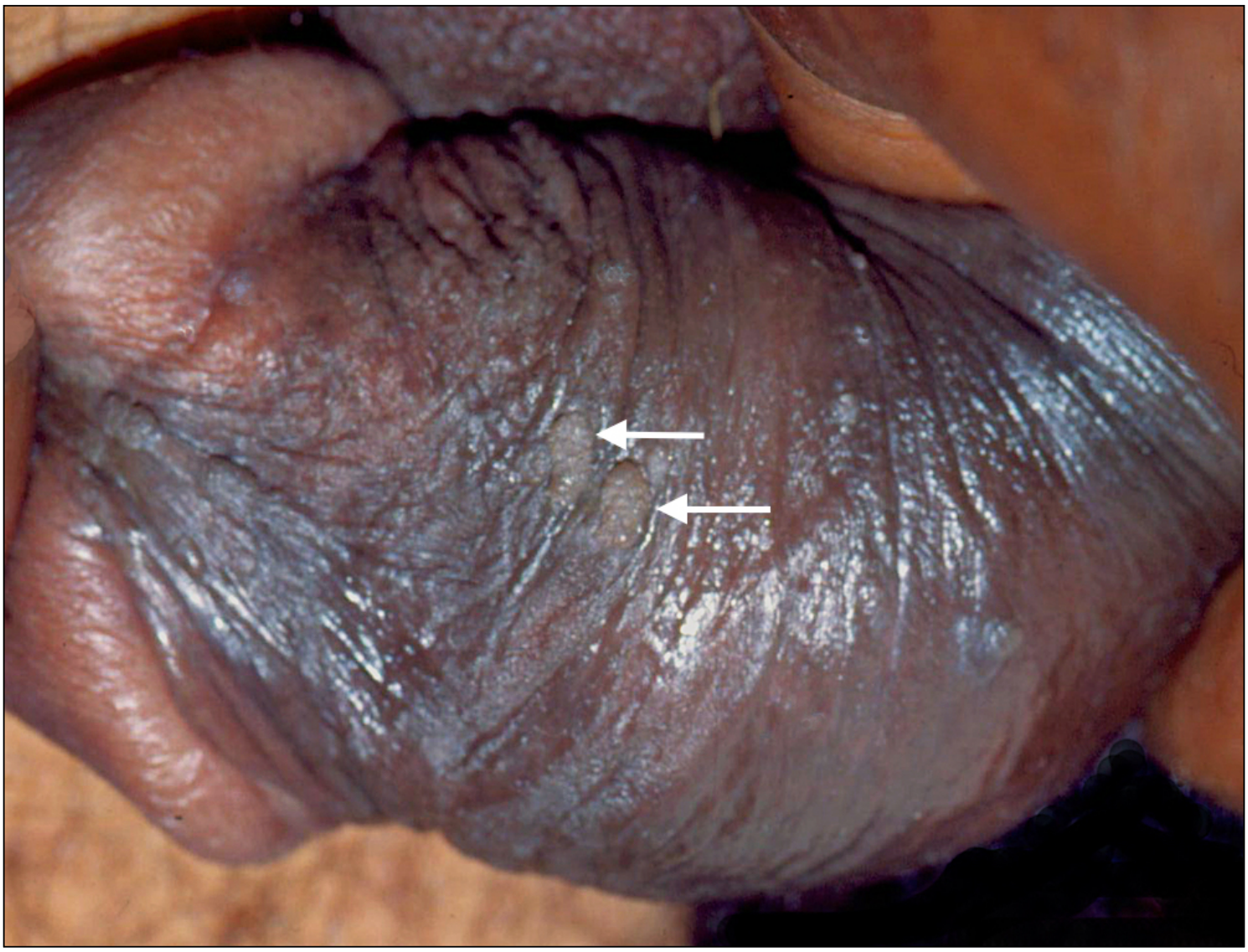

Table 1. STI Screening Recommendations in Persons with HIV

Table 1.

STI Screening Recommendations in Persons with HIV

STI	Screening Indications and Frequency
Chlamydia	• For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter • More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology
Gonorrhea	• For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter • More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology
Syphilis	• For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter • More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology
Herpes	• Type-specific herpes simplex virus (HSV) serologic screening for HSV-2 should be considered for persons presenting for an STI evaluation (especially for those persons with multiple sex partners)
Trichomoniasis	• Recommended for sexually active women at entry to care and at least annually thereafter
HPV, Cervical Cancer	• Sexually active women with HIV who are at least 21 years of age should undergo cervical cancer screening at initial entry to HIV care and again 12 months later. • Annual Pap testing is recommended in women with HIV younger than 30 years of age, but if 3 consecutive annual screens are normal, Pap tests can be performed every 3 years. • Women with HIV who are 30 years of age and older should have either (1) cervical cancer screening by Pap testing alone or (2) Pap testing plus simultaneous HPV co-testing. If Pap testing alone is used, it should be performed at baseline and every 12 months; if the results of 3 consecutive Pap tests are normal, then follow-up testing can occur every 3 years. If Pap and HPV co-testing is performed and both are negative, follow-up screening can be performed in 3 years. • Cervical cancer screening should continue throughout the life in women with HIV.
Anal Cancer	• Digital anorectal exam

STI	Screening Indications and Frequency
	• Screen men who have sex with men with HIV who are 35 years of age and older and screen all others with HIV who are 45 years of age and older. Specific screening recommendations depend on availability of high resolution anoscopy (HRA).
Hepatitis B Screening	• At the initial evaluation, test for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core (anti-HBc), and hepatitis B surface antibody (anti-HBs)
Hepatitis C Screening	• At the initial evaluation, perform serologic testing for antibody to HCV (anti-HCV), with reflex to HCV RNA for all positive anti-HCV tests • Annual HCV serologic testing in men who have sex with men* • For persons with prior spontaneous or treatment clearance of HCV, screening should be conducted with HCV RNA
*These recommendations are for STI screening. Screening for hepatitis C also should be done at least annually in people who inject drugs. **NOTE**: This table is modified from recommendations in the Centers for Disease Control 2021 Sexually Transmitted Infections Treatment Guidelines and the 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.	

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. Human papillomavirus disease. July 9, 2024. [HIV.gov]
- Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Screening Recommendations and Considerations Referenced in Treatment Guidelines and Original Sources. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 8. Treatment of Acyclovir-Resistant Mucocutaneous HSV Infection

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
- Topical foscarnet 1% five times a day

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.
- An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir-resistant HSV infection; for more information see Aicuris Pritelivir Early Access website.

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 Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America. Herpes simplex virus. Last updated: July 14, 2025. [HIV.gov]