Syphilis

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Epidemiology

Syphilis, caused by *Treponema pallidum*, is associated with an increased risk of sexual acquisition and transmission of HIV.[1-9] While rates remain high, from 2023 to 2024, the rate of reported primary and secondary syphilis cases in the United States decreased overall and among both men and women. A substantial increase in the rate of reported congenital syphilis cases occurred from 2015 to 2024.[10,11] Although HIV infection, particularly in the advanced stages, may modify the natural history or clinical manifestations of *T. pallidum* infection, the principles of syphilis management remain the same for people with and without HIV.[2,12-17]

Clinical Manifestations

In most people with HIV and syphilis, the clinical manifestations of syphilis are similar to those observed in people without HIV. However, some studies suggest that infection with HIV can affect the clinical presentation of syphilis: for example, atypical, painful, or multiple genital ulcers may be more apparent in some. Accelerated progression of syphilis may be seen in people with advanced immunosuppression.[14,15,18-22] Primary or secondary syphilis may cause a transient decrease in CD4 T lymphocyte (CD4) cell count and a transient increase in HIV viral load, which improves with recommended syphilis treatment regimens.[2,23-27] Independent of HIV, previous syphilis can attenuate the clinical and laboratory manifestations of incident reinfection with *T. pallidum*.[28-30]

Primary syphilis commonly presents as a single painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, multiple or atypical painful chancres may occur (also, in some, pain might be due to coinfection with herpes simplex virus), and primary lesions may be absent or missed by the patient and on physical examination.[14,20,31] Progression to secondary syphilis typically follows 2 to 8 weeks after primary syphilis, but an overlap in primary and secondary manifestations can occur, especially in people with HIV.[32] The most common manifestations of secondary syphilis are mucocutaneous lesions that are macular, maculopapular, papulosquamous, or pustular. These lesions can involve the palms and soles and are often accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache.[2,15,16] Mpox lesions can have a similar appearance and can occur simultaneously with early syphilis.[33] Condylomata lata (moist, flat papular lesions in warm intertriginous regions) can occur and may resemble condylomata acuminata caused by human papillomavirus. Mucous patches (usually involving the oral mucosa) and patchy alopecia may also be present. Lues maligna is an uncommon manifestation of secondary syphilis, characterized by papulopustular skin lesions that can evolve into ulcerative lesions with sharp borders and a dark central crust.[34-36] Manifestations of secondary syphilis involving other locations can occur (e.g., ocular and otic syphilis, meningoencephalitis, hepatitis, nephrotic syndrome, gastritis, pneumonia). Non-focal central nervous system (CNS) symptoms and cerebrospinal fluid (CSF) abnormalities, such as lymphocytic pleocytosis with a mildly elevated CSF protein, can often occur with secondary syphilis.[18,21,31,37-41] Signs and symptoms of primary and secondary syphilis can overlap or persist from a few days to several weeks before resolving. In some instances, if untreated, recrudescence of symptoms may occur after secondary syphilis, with subsequent evolution to latent stages. Those with previous syphilis infections may be more likely to be

asymptomatic or have subtle signs or symptoms with a subsequent infection; the threshold for testing should be low in these individuals.[42-44]

Latent syphilis is defined as serologic reactivity without clinical signs and symptoms of infection. Latent syphilis can be categorized as early latent syphilis if ≤1 year duration, late latent syphilis if >1 year duration, or latent syphilis of unknown duration if there is insufficient information to determine the duration of infection. Early latent syphilis may occur between the primary and secondary stages or following resolution of the signs and symptoms of secondary syphilis. Tertiary syphilis refers to symptomatic manifestations that occur one year or more following infection and these include gummas, cardiovascular syphilis, or late neurosyphilis (general paresis, tabes dorsalis) that can develop even decades after untreated infection.

Neurosyphilis can occur at any stage of syphilis with different clinical presentations, including, but not limited to, cranial nerve dysfunction, meningitis, stroke, acute or chronic change in mental status, and loss of vibration sense. Manifestations of neurosyphilis in people with HIV are similar to those in individuals who do not have HIV. However, clinical manifestations of neurosyphilis, such as ocular syphilis (including uveitis) or meningitis during early syphilis may be more common in people with HIV.[2,18,21,41,45-50]

Ocular syphilis with syphilitic uveitis or other ocular syphilis manifestations (e.g., neuroretinitis. optic neuritis) can occur during any stage of syphilis and can manifest as isolated abnormalities or can be associated with neurosyphilis. Syphilis can involve almost any ocular structure, but posterior uveitis and panuveitis are the most common presentations. Other common manifestations can include interstitial keratitis, recurrent anterior uveitis, retinal vasculitis, and optic neuropathy.[51] Otosyphilis, which may manifest as isolated hearing loss or other otologic symptoms (e.g., tinnitus, vertigo), can occur at any stage of syphilis and can be associated with neurosyphilis. Left untreated, ocular and otic syphilis may lead to permanent deficits.

Diagnosis

Diagnostic considerations for syphilis in people with HIV are the same as for people without HIV and therefore align with those outlined in the Sexually Transmitted Infection (STI) Treatment Guidelines of the Centers for Disease Control and Prevention (CDC) and the CDC Laboratory Recommendations for Syphilis Testing. A summary is provided below.

Direct Detection

Darkfield microscopy and molecular tests to detect *T. pallidum* in lesion exudates or tissue (e.g., biopsy with silver stain) are definitive for diagnosing primary or secondary syphilis.[52,53] *T. pallidum* direct fluorescent antibody testing is not commercially available; however, immunohistochemistry and silver staining tests may be offered by some laboratories. A variety of direct nucleic acid amplification tests have been developed for use on different specimen types; however, none are cleared by the U.S. Food and Drug Administration (FDA).[53]

Serologic Testing

Serologic diagnosis of syphilis traditionally has involved screening for nontreponemal antibodies against cardiolipin and other lipoidal antigens in *T. pallidum* and which are also released by host cells, with confirmation of reactive tests by treponemal-based assays which detect antibodies to

lipoproteins that are specific to the spirochete (i.e., the "traditional algorithm").[2,53-56] The "reverse-sequence algorithm," which starts with treponemal antibody tests followed by confirmation with nontreponemal antibody tests, is also used. In this algorithm, if the lipoidal antibody is negative, a second and different treponemal antibody serves as a tie breaker. Each algorithm has advantages and disadvantages, but either is acceptable for the diagnosis of syphilis in most people with HIV.[53]

- Nontreponemal tests (or 'lipoidal' tests): Rapid plasma reagin (RPR), Venereal Disease Research Laboratory test (VDRL)
- Treponemal tests: Enzyme immunoassays (EIAs), chemiluminescence immunoassays (CIAs), *T. pallidum* particle agglutination (TP-PA), multiplex flow (microbead) immunoassays, fluorescent treponemal antibody absorption (FTA-ABS), immunoblots

Rapid treponemal assays (including a recently FDA-approved home test) are also available to screen for syphilis using fingerstick whole blood; however, positive results on treponemal tests cannot differentiate recent or past infection, so testing with a nontreponemal test is needed to inform further patient management.[2,53-55,57,58] Use of only one type of serologic test (nontreponemal or treponemal) is insufficient for diagnosis and can result in false-positive or false-negative results. For a comprehensive discussion of serologic testing and each algorithm, refer to the CDC STI Treatment Guidelines and CDC Laboratory Recommendations for Syphilis Testing.

Additional Diagnostic Considerations by Syphilis Stage

Early-Stage Syphilis

Early-stage disease (i.e., primary, secondary, and early latent syphilis) is identified with the same diagnostic tests used in people without HIV: standard serologic tests, darkfield microscopy, or nucleic acid amplification tests (NAATs) of mucocutaneous lesions, if available. RPR titers or VDRL titers may be higher, lower (in rare instances), or delayed in people with HIV and early-stage syphilis.[59-63] No data indicate that treponemal tests perform differently among people with HIV[55]; however, although uncommon, false-negative serologic tests for syphilis can occur with documented *T. pallidum* infection.[62,63] Irrespective of HIV status, antibodies may take a week or more to develop. Both nontreponemal and treponemal tests might not yet be reactive in persons with early primary syphilis, although some treponemal tests may be reactive earlier than nontreponemal tests.[64] When serologic tests do not correspond with clinical findings indicative of syphilis (e.g., primary or secondary syphilis), presumptive treatment is recommended for people with risk factors for syphilis. In this circumstance, additional testing should also be considered, including assessing for the prozone phenomenon (an excess of patient antibodies that prevents the formation of a precipitate) by diluting the sample, repeating serologies after 2 to 4 weeks, and using other tests (e.g., biopsy for histology and immunostaining or lesion swab for polymerase chain reaction).[2,53,65,66] For most people with HIV, serologic tests are accurate and reliable for diagnosing early syphilis and determining response to treatment.[2,53,66]

Latent Syphilis

By definition, people with latent syphilis have serological evidence of syphilis in the absence of clinical manifestations. Early latent syphilis may occur in the interval between the primary and secondary stage of infection or following resolution of secondary manifestations and may be defined by evidence of infection during the preceding year by:

- A documented seroconversion or sustained fourfold or greater increase in nontreponemal titer; *or*
- Symptoms of primary or secondary syphilis; *or*
- A sex partner with documented primary, secondary, or early latent syphilis.[2]

Late latent syphilis is defined as syphilis in a person who does not have evidence of having acquired infection during the preceding year. Latent syphilis of unknown duration is defined as latent syphilis with insufficient evidence to determine duration of infection.

Neurosyphilis, Ocular Syphilis, and Otic Syphilis

All people with syphilis who exhibit signs or symptoms suggesting neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke, altered mental status) warrant evaluation for neurosyphilis with CSF examination. CSF abnormalities (i.e., elevated protein and mononuclear pleocytosis) are common in early-stage syphilis,[37,67] as well as in people with HIV, even in those with no neurologic symptoms. The clinical and prognostic significance of CSF laboratory abnormalities with early-stage syphilis in people without neurologic symptoms is unknown. Several studies have demonstrated that in people with syphilis and HIV, CSF laboratory abnormalities are associated with CD4 counts ≤350 cells/mm^3 or in combination with RPR titers ≥1:32.[68,69] However, unless neurologic signs or symptoms are present, a CSF examination has not been associated with improved clinical outcomes.

Although laboratory testing is helpful in supporting the diagnosis of neurosyphilis, no single test can be used to diagnose neurosyphilis. Diagnostic considerations for neurosyphilis in people with HIV are similar to those for people without HIV and are in alignment with those outlined in the CDC STI Treatment Guidelines, as summarized below.

The diagnosis of neurosyphilis depends on a combination of CSF tests (e.g., CSF cell count, CSF protein, and CSF-VDRL), reactive serologic test results, and neurologic signs or symptoms. CSF examination may indicate mononuclear pleocytosis (>5 cells/mm^3), elevated protein concentration, or a reactive CSF-VDRL. Among people with HIV, the CSF leukocyte count can be elevated (CSF white blood count >5 cells/mm^3); in people not on antiretroviral therapy (ART), using a higher cutoff (>20 cells/mm^3) may improve the specificity of neurosyphilis diagnosis.[40] In people with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not visibly contaminated with blood) is considered diagnostic of neurosyphilis; however, it is thought to have a low sensitivity and therefore may miss true disease. Therefore, in the right clinical context (e.g., neurologic signs or symptoms, reactive peripheral serologies, elevated CSF white blood cell [WBC] count or protein), neurosyphilis should be considered even when the CSF-VDRL is nonreactive. In that instance, additional evaluation using CSF treponemal antibody testing may be considered.[2] There are no FDA-cleared CSF treponemal antibody tests; however, the CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Thus, a reactive CSF FTA-ABS test cannot be used to support a diagnosis of neurosyphilis, but a nonreactive test makes the diagnosis unlikely. Fewer data are available regarding CSF TP-PA; however, the sensitivity and specificity appears similar to the CSF FTA-ABS.[70,71] Neurosyphilis is highly unlikely with a negative CSF FTA-ABS or TP-PA test, especially among people with nonspecific neurologic signs and symptoms. Data are limited and conflicting regarding the performance of RPR tests in the CSF, but at least one study showed a high false-negative rate.[72-74] NAAT-based diagnostic methods **are not currently recommended** as diagnostic tests for neurosyphilis because of their low sensitivity, and none are cleared by the FDA for use on CSF.

All people with ocular symptoms and reactive syphilis serologies need a full ocular examination, including cranial nerve evaluation. If cranial nerve dysfunction is present, a CSF evaluation is needed. Among people with isolated ocular symptoms (no cranial nerve dysfunction or other neurologic abnormalities), reactive syphilis serologies, and confirmed ocular abnormalities on examination, CSF examination is unnecessary before treatment for ocular syphilis. CSF analysis might be helpful in evaluating people with ocular symptoms and reactive syphilis serologies who do not have ocular findings on examination. If ocular syphilis is suspected, immediate referral to and management in collaboration with an ophthalmologist is crucial, however initiation of treatment need not be delayed until patients are seen by an ophthalmologist. Ocular syphilis should be treated similarly to neurosyphilis, even if a CSF examination is normal, because ocular syphilis may occur in the absence of CSF abnormalities.

Among people with isolated auditory abnormalities and reactive syphilis serologies, CSF evaluation is likely to be normal and is not necessary before treatment for otosyphilis. Otosyphilis should be managed in collaboration with an otolaryngologist and treated similarly to neurosyphilis.[75]

Preventing Exposure and Disease

Risk Assessment and Counseling

The resurgence of syphilis and other STIs underscores the importance of primary prevention of syphilis, which should begin with a behavioral risk assessment and routine discussion of sexual behaviors. Health care providers should discuss patient-centered risk reduction messages and advise specific actions that can reduce the risk of acquiring STIs and of transmitting HIV.[2,76-80] The occurrence of incident syphilis or any other STI in a person with HIV is an indication of behaviors that should prompt intensified risk assessment and counseling messages about the manifestations of syphilis, risk of HIV transmission, and prevention strategies with strong consideration for behavioral intervention (e.g., condom use).[81,82]

Routine Screening

Routine serologic screening for syphilis is recommended at least annually for all people with HIV who are sexually active, with more frequent screening (every 3–6 months) for those with risk factors, such as multiple or anonymous sexual partners or new partners **(AII).**[2,83-87] Frequent serologic screening can identify people with recent infection and, in some instances, before infectious lesions develop. Treatment can prevent disease progression in the individual and transmission to their partners or fetus. People undergoing screening or treatment for syphilis also should be evaluated for other STIs as clinically indicated.[2,88]

Management of Sexual Partners After Exposure to Syphilis

Presumptive Treatment of Sexual Partners After Exposure to *Treponema pallidum* (Syphilis)
Indications for Presumptive Treatment • Sex partner diagnosed with primary, secondary, or early latent syphilis o Individuals exposed sexually ≤90 days before the partner's diagnosis should be presumptively treated for early syphilis, regardless of syphilis serologic status (AII). o Individuals exposed sexually >90 days before the partner's diagnosis should be presumptively treated if syphilis serologic test results are not available immediately and the opportunity for follow-up is uncertain (AIII). Presumptive Treatment • Same as therapy for "Primary, Secondary, and Early Latent Syphilis" in the Recommendations for Treating Syphilis table.

Studies in the pre-HIV era demonstrated that approximately one-third of the sexual partners of people who have primary syphilis will develop syphilis within 30 days of exposure; presumptive treatment of sexual partners exposed to syphilis will prevent the development of disease and onward syphilis transmission.[89-92] Individuals who have had recent sexual contact with a person with any stage of syphilis should be evaluated clinically and serologically. Screening considerations for people with HIV who were exposed to syphilis through their partner are the same as for people without HIV and are in alignment with those in the CDC STI Treatment Guidelines, as outlined below.

- People who have had sexual contact with an individual diagnosed with primary, secondary, or early latent syphilis during the 90 days preceding that individual's diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative **(AII).**
- Sexual partners who have had sexual contact with an individual who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before that individual's diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain **(AIII).** If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and the stage of syphilis.
- Long-term sexual partners of people who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings.
- Sexual partners of people with syphilis should be notified of their exposure and the importance of evaluation for testing and empiric therapy.[2] The following sex partners of people with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation. Partners who have had sexual contact within:
    1. Three months plus the duration of symptoms for people who receive a diagnosis of primary syphilis,
    2. Six months plus the duration of symptoms for those diagnosed with secondary syphilis,
    3. One year for people diagnosed with early latent syphilis.

Post-exposure Prophylaxis for Prevention of Bacterial Sexually Transmitted Infections, Including Syphilis

Doxycycline post-exposure prophylaxis (abbreviated as "doxy PEP" and administered as 200 mg PO once within 72 hours of condomless sex) reduces incidence of syphilis, chlamydia, and, in some studies, gonorrhea in men who have sex with men (MSM) and transgender women (TGW).[93-103] One randomized controlled trial found a reduction in a combined outcome of incident gonorrhea, chlamydia, and syphilis in MSM and TGW with HIV, as well as in those on HIV pre-exposure prophylaxis (PrEP).[104] Other studies are underway or in development regarding doxy PEP or PrEP for these three bacterial STIs.[94]

For comprehensive guidance on prescribing, counseling, STI testing, and monitoring, providers should reference the CDC Doxycycline PEP Guidelines.[100] In brief, these guidelines advise providers to counsel all gay, bisexual, and other MSM and TGW (including those with HIV) with a history of at least one bacterial STI (specifically, syphilis, chlamydia, or gonorrhea) during the past 12 months about the benefits and harms of using doxy PEP for bacterial STI (including syphilis) prevention and offer doxy PEP through shared decision-making.[105] Doxy PEP may affect the diagnosis of syphilis regarding either clinical presentation or serologic response.[106]

Treating Disease

Recommendations for Treating Syphilis
General Considerations for Treating Syphilis
• Selection of the appropriate penicillin preparation should be based on the stage of disease because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly penetrated by certain forms of penicillin. • Combinations of benzathine penicillin and procaine penicillin or short-acting benzathine-procaine penicillin (Bicillin C-R) preparations are not appropriate for syphilis treatment. • In the setting of drug shortages, refer to the FDA's Drug Shortages and CDC's Availability of STI Testing and Treatment Products webpages for information and alternatives. Procaine penicillin has been discontinued by the manufacturer as of June 13, 2023. • The efficacy of non-penicillin alternatives has not been well evaluated in people with HIV and should be undertaken only with close clinical and serologic monitoring. Azithromycin **should not be used** as treatment for syphilis (AII). • The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache, fever, and myalgias that can occur within the first 24 hours after therapy. It occurs more frequently in people with early syphilis and can induce early labor or cause fetal distress during pregnancy. Patients should be informed about this potential reaction to treatment and that it is not an allergic reaction to penicillin.
Treating *Treponema pallidum* Infections (Syphilis) Based on Stage of Disease
Primary, Secondary, and Early Latent Syphilis (≤1 year) *Preferred Therapy* • Benzathine penicillin G 2.4 million units IM in a single dose (AII)

Alternative Therapy

- Doxycycline 100 mg PO twice daily for 14 days (BII), *or*
- Ceftriaxone 1 g IM or IV daily for 10–14 days (BII)

Note: People with penicillin allergy whose adherence or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G[a] (AIII).

Late Latent (>1 year) or Latent of Unknown Duration

Preferred Therapy

- Benzathine penicillin G 2.4 million units IM weekly for three doses (AII)

Alternative Therapy

- Doxycycline 100 mg PO twice daily for 28 days (BIII)

Note: People with penicillin allergy whose adherence to oral therapy cannot be ensured should be desensitized and treated with benzathine penicillin G[a] (AIII).

Tertiary—Cardiovascular or Gummatous Disease

- Due to the complexity of tertiary syphilis management, health care providers are advised to consult an infectious diseases specialist.
- Consider CSF examination. People with CSF abnormalities should be treated with a regimen for neurosyphilis (AII).

Preferred Therapy

- For people without neurosyphilis: Benzathine penicillin G 2.4 million units IM weekly for three doses (AII)

Penicillin-Allergic Patients[a]

- Treat in consultation with infectious diseases specialist.

Neurosyphilis, Ocular Syphilis, or Otic Syphilis

Preferred Therapy

- Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or by continuous IV infusion for 10–14 days (AII)[b]

Alternative Therapy

- Procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg PO four times a day for 10–14 days (BII). However, procaine penicillin has been discontinued by the manufacturer as of June 13, 2023.
- Note: People who are allergic to sulfa-containing medications should not be given probenecid; thus, IV penicillin is recommended (AIII).

Penicillin-Allergic Patients[a]

- *Preferred Therapy:* Desensitization to penicillin
- *Alternative Therapy:* Ceftriaxone 2 g IM or IV daily for 10–14 days (BII)
    - Limited data suggest ceftriaxone may be an option for treatment of neurosyphilis with patient–provider shared decision-making. The risk for penicillin cross-reactivity between third-generation cephalosporins is low. If substantial concern exists regarding ceftriaxone safety for a patient with penicillin allergy and neurosyphilis, consultation with a specialist is recommended; graded ceftriaxone challenge or skin testing to confirm penicillin allergy and, if necessary, penicillin desensitization may be needed.

Pregnancy Considerations
• Penicillin G is recommended for the treatment of syphilis during pregnancy; pregnant women should be treated with the recommended regimen for their clinical stage of disease as above (AIII). • Erythromycin and azithromycin should not be used (AII); tetracyclines are not recommended for the treatment of syphilis during pregnancy (AII). • If multiple doses of benzathine penicillin are required (i.e., for late latent syphilis), the interval between doses should not exceed 9 days. If the interval exceeds 9 days, restarting the regimen is recommended (BII). Penicillin-Allergic Patients[a] • Penicillin skin testing and/or oral graded challenge may be helpful in identifying those at risk for acute allergic reactions (BII). • For those who have a history of more serious reactions, skin testing with oral challenge is not recommended; pregnant women should undergo penicillin desensitization in the intensive care unit with appropriate referral services and fetal monitoring prior to and after the therapeutic dose is administered (BII). Subsequent indicated doses can be administered in the outpatient setting due to the prolonged half-life of IM benzathine penicillin G if administered within the appropriate interval (CIII).

[a] Skin testing for penicillin allergy can be useful in circumstances in which the reagents and expertise are available. Among people for whom the only option is penicillin (e.g., syphilis in pregnancy) and among those with a positive skin test, desensitization to penicillin in consultation with a specialist is the preferred approach. Skin testing, challenge, and desensitization may be contraindicated in patients with certain severe adverse reactions (e.g., Stevens-Johnson Syndrome, toxic epidermal necrolysis, interstitial nephritis, hemolytic anemia). These patients should be managed in consultation with an allergist and infectious diseases specialist.

[b] There are no data on the effectiveness of additional intramuscular doses of benzathine penicillin G 2.4 million units after completion of aqueous crystalline penicillin G infusion.

Key: CDC = Centers for Disease Control and Prevention; CNS = central nervous system; CSF = cerebrospinal fluid; FDA = U.S. Food and Drug Administration; IM = intramuscularly; IV = intravenously; PO = orally; STI = sexually transmitted infection

Primary, Secondary, and Early Latent Syphilis

Treatment regimens for syphilis demonstrate that most people with HIV respond appropriately to single dose benzathine penicillin G after exposure to syphilis and for primary, secondary, and early latent syphilis.[2,60,107,108] However, in people with HIV, more frequent clinical and serologic evaluation is recommended—every 3 months rather than every 6 months—because serologic nonresponse and neurologic complications may be more frequent.[18,109,110] Use of ART in people with syphilis and HIV has also been associated with a reduced risk of serologic failure of syphilis treatment and a lower risk of developing neurosyphilis.[21]

Benzathine penicillin G remains the treatment of choice for syphilis. People with HIV with early-stage (primary, secondary, or early latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million units of benzathine penicillin G **(AII).** There is no evidence that three doses of benzathine penicillin G is more efficacious than one dose of benzathine penicillin for early syphilis in people with HIV.[2,111] High-dose amoxicillin given with probenecid in addition to benzathine penicillin G in early syphilis is not associated with improved clinical outcomes.[60] People with a penicillin allergy whose adherence with oral therapy (see below) or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G **(AIII).**

The use of any alternative treatment regimen should be undertaken only with close clinical and serologic monitoring.[2,112] Alternative therapy for nonpregnant adults includes doxycycline, 100 mg orally twice daily for 14 days, to treat early syphilis **(BII).**[2,113,114] Based on limited clinical studies in

people with and without HIV, ceftriaxone (1 g daily either IM or intravenously [IV] for 10–14 days) could be used for treating early syphilis **(BII),** but the optimal dose and duration of therapy have not been defined.[115,116] Limited data suggest a single 2-g dose of oral azithromycin can be effective for treating early syphilis[117-119]; however, *T. pallidum* chromosomal mutations associated with azithromycin resistance are highly prevalent and treatment failures have been reported—most commonly in MSM.[120-126] Azithromycin has not been well studied in people with HIV or during pregnancy. Therefore, azithromycin **should not be used** as treatment for syphilis **(AII).** Other alternative antibiotic regimens are under evaluation, but evidence is presently insufficient to recommend their use.[127]

Late Latent Syphilis

In people with HIV who have late latent syphilis (including latent syphilis of unknown duration), treatment with three weekly IM injections of 2.4 million units of benzathine penicillin G is recommended **(AII).** Alternative therapy for nonpregnant adults is doxycycline, 100 mg orally twice daily for 28 days **(BIII);** however, this regimen has not been well evaluated in people with HIV. Limited clinical studies and biologic and pharmacologic evidence suggest that ceftriaxone may be effective, but the optimal dose and duration of therapy have not been determined.[128,129] If the clinical situation requires use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring. People with a penicillin allergy whose adherence to oral therapy cannot be ensured should ideally be desensitized and treated with benzathine penicillin G **(AIII).** Additional desensitization challenges following the administration of the initial dose of benzathine penicillin G are not necessary if subsequent doses are administered within the recommended interval.

Tertiary Syphilis

People with HIV who have clinical evidence of cardiovascular or gummatous disease should be considered for CSF examination to rule out CSF abnormalities. People with CSF abnormalities should be treated with a regimen for neurosyphilis **(AII).** If the CSF evaluation is normal, the recommended treatment of late-stage syphilis is three weekly IM injections of 2.4 million units of benzathine penicillin G **(AII).**[2] However, due to the complexity of tertiary syphilis management, especially cardiovascular syphilis or in people with penicillin allergy, health care providers are advised to consult an infectious diseases specialist.

Neurosyphilis, Ocular Syphilis, and Otic Syphilis

People with HIV diagnosed with neurosyphilis, ocular syphilis, or otic syphilis should receive IV aqueous crystalline penicillin G (18–24 million units daily, administered 3 to 4 million units IV every 4 hours or by continuous infusion for 10–14 days) **(AII).** Procaine penicillin G (2.4 million units IM once daily plus probenecid 500 mg orally four times a day for 10–14 days) was considered an alternate treatment **(BII),** but procaine penicillin has been discontinued by the manufacturer since June 13, 2023. People with HIV who are allergic to sulfa-containing medications **should not be given** probenecid because of potential allergic reaction; therefore, IV penicillin is recommended **(AIII).**

Although systemic steroids are used frequently as adjunctive therapy for otic syphilis, in theory, to reduce inflammation related sequelae, robust studies supporting such therapy are not available.[130]

Because neurosyphilis treatment regimens are of shorter duration than those used in late latent syphilis, 2.4 million units of benzathine penicillin IM once after completion of IV penicillin G is sometimes administered to provide a comparable duration of therapy; however, no comparative studies support this approach.[2]

Alternative Regimens, Including in People With Penicillin Allergy

In people with penicillin allergy, desensitization is preferred. Limited data suggest ceftriaxone (2 g IM or IV daily for 10–14 days) may be an option for treatment of neurosyphilis with patient–provider shared decision-making **(BII).**[115,129,131] Other alternative regimens for neurosyphilis have not been evaluated adequately.[132,133] The risk for penicillin cross-reactivity between third-generation cephalosporins and penicillin is low. However, if substantial concern exists regarding safety of ceftriaxone in a patient with penicillin allergy, consultation with a specialist is recommended; ceftriaxone graded challenge or skin testing to confirm penicillin allergy and, if necessary, penicillin desensitization may be needed. Penicillin skin testing, challenge, and desensitization **may be contraindicated** in patients with certain severe adverse reactions (e.g., Stevens-Johnson Syndrome, toxic epidermal necrolysis, interstitial nephritis, hemolytic anemia). These patients should be managed in consultation with an allergist and ID specialist. Syphilis treatment recommendations and additional resources for managing penicillin allergy are available in the CDC STI Treatment Guidelines.

Special Considerations Regarding Antiretroviral Therapy Initiation

There are no special considerations regarding the initiation of ART in people with HIV and syphilis. Specifically, there is no evidence that treatment with ART needs to be delayed until treatment for syphilis has been completed. Immune reconstitution inflammatory syndrome in association with syphilis following treatment with ART in people with HIV is uncommon.[134,135]

Monitoring and Adverse Events

Clinical and serologic responses to treatment are similar in people with HIV; subtle variations can occur, however, including a slower pattern of serologic response in people with HIV.[2,60,89,107,108] Factors associated with favorable serologic response to treatment in people without HIV include younger age, earlier syphilis stage, and higher RPR titer.[136-138] Serologic response to treatment is defined as a fourfold decrease from the nontreponemal titer at the time of treatment (e.g., 1:16 to 1:4). The potential for reinfection should be based on the sexual history and risk assessment.

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, rigors, transient worsening of rash, myalgia, and sometimes even a sepsis-like syndrome, that can occur within the first 24 hours after initiation of treatment for syphilis. Antipyretics can be used to manage symptoms but have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction occurs most frequently in people with early syphilis, high nontreponemal antibody titers, and prior penicillin treatment; rates can be lower in people with HIV than in people without HIV, but are still substantial.[139,140] People with syphilis should be warned about this reaction, instructed how to manage it, and informed that it is not an allergic reaction to penicillin. Careful communication and a preemptive plan should be provided to pregnant women.

Primary and Secondary Syphilis

Clinical and serologic responses to treatment of primary and secondary disease should be assessed at 3, 6, 9, 12, and 24 months after therapy to ensure resolution of signs and symptoms and an appropriate serological response. In people with HIV, signs and symptoms should resolve, and seroreversion (where the lipoidal test becomes negative) or a fourfold decline in nontreponemal titers should occur within 24 months. If clinical signs and symptoms persist, treatment failure should be considered. If clinical signs or symptoms recur or there is a sustained fourfold increase in nontreponemal titers over 2 weeks, treatment failure or reinfection should be considered and managed per recommendations (see Managing Possible Treatment Failure or Reinfection section below).

Clinical trial data have demonstrated that up to 20% of people (including people with HIV) treated with recommended therapy for early-stage syphilis will not achieve the fourfold decline in nontreponemal titer used to define treatment response at 1 year.[2,60] In addition, people treated for syphilis who have a fourfold decline in titer may not serorevert to a nonreactive nontreponemal test.[141,142]

Latent Syphilis

Response to therapy for latent syphilis should be monitored using nontreponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a fourfold decline in titer within 24 months of therapy. However, data to define the precise time intervals for adequate serologic responses are limited. Many people with low titers (<1:8) and late latent syphilis do not have a fourfold decline in the initial titer. If clinical symptoms develop or a fourfold increase in nontreponemal titers is sustained over 2 weeks, then treatment failure or reinfection should be considered and managed per recommendations (see Managing Possible Treatment Failure or Reinfection section below).

Neurosyphilis

The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF WBC. The CSF-VDRL may respond more slowly. Limited data suggest that changes in CSF parameters may occur more slowly in people with HIV, especially with advanced immunosuppression.[21,40] Among people with HIV who are receiving effective ART, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment.[143,144] Therefore, repeated CSF examinations are unnecessary for people with HIV who are on ART at the time of neurosyphilis treatment and who exhibit serologic and clinical responses after neurosyphilis treatment.[2]

Managing Possible Treatment Failure or Reinfection

Retreatment should be considered for people with early-stage syphilis who have recurring clinical signs or symptoms of disease, or a sustained fourfold increase in serum nontreponemal titers after an initial fourfold decrease following treatment if reinfection seems likely. The assessment for potential reinfection should be informed by a sexual history and syphilis risk assessment, including information about any recent sexual partners with signs or symptoms or recent treatment for syphilis. The current nontreponemal titer should be compared to the titer prior to the last treatment.

People with HIV may be at increased risk of treatment failure, but the magnitude of these risks is not precisely defined and is likely low.[2,39,110] However, people with primary or secondary syphilis who have signs or symptoms that persist or recur, or a have a fourfold increase or greater in titer sustained

for more than 2 weeks, and are at low risk for reinfection should be managed for possible treatment failure. A CSF evaluation is recommended, with findings guiding management. People with HIV with nontreponemal titers that do not decrease at least fourfold within 24 months of therapy for early syphilis could also be experiencing treatment failure. Management includes a thorough history and examination for ocular, otic, or neurologic signs and symptoms and consideration of CSF examination and retreatment. If the CSF examination is concerning for neurosyphilis (see Diagnosis section above), appropriate neurosyphilis treatment should be given. If the CSF examination is not consistent with neurosyphilis treatment with benzathine penicillin G, 2.4 million units at 1-week intervals for 3 weeks should be given **(BIII).** If titers do not respond appropriately after retreatment, the value of repeated CSF examination or additional therapy is unclear, but it **is generally not recommended.** People with recurrent signs and symptoms of primary or secondary syphilis, or a fourfold increase in nontreponemal titers, and at high risk of syphilis reinfection, should be given benzathine penicillin treatment (2.4 million units IM) without a CSF examination (unless signs or symptoms of neurosyphilis are present), and close clinical follow-up is recommended **(CIII).**

People treated for latent syphilis should have a CSF examination and be retreated if they develop clinical signs or symptoms of syphilis or have a sustained fourfold increase in serum nontreponemal test titer and are at low risk for reinfection. A CSF examination may be considered if they experience an inadequate serologic response (i.e., less than fourfold decline at 24 months), particularly if there was an initially high titer (>1:32). If the CSF examination is consistent with CNS involvement (see the Diagnosis section above), or if there is concern for otic or ocular syphilis, retreatment should follow the recommendations for treatment of neurosyphilis. People with a normal CSF examination who do not have ocular or otic symptoms should be treated with benzathine penicillin 2.4 million units IM weekly for three doses **(BIII).**

Special Considerations During Pregnancy

Lack of timely testing and adequate treatment contributed to almost 90% of congenital syphilis cases in the United States in 2022.[11] Pregnancy does not appear to alter the clinical course, manifestations, or diagnostic test results for syphilis infection in adults. The clinical manifestations of syphilis in pregnancy are similar in people with and without HIV. Syphilis in pregnancy is associated with an increased risk of several adverse outcomes, including pregnancy loss, stillbirth, impaired fetal growth, and significant neonatal morbidity and mortality resulting from abnormalities in multiple organ systems. Transmission to the fetus and adverse pregnancy outcomes for untreated syphilis can occur at any time during pregnancy and are highest with primary, secondary, and early latent syphilis, decreasing but possible with late-stage infection. In general, the risk of antepartum fetal infection or congenital syphilis at delivery is associated with the stage of maternal infection and the quantitative maternal nontreponemal titer, especially if ≥1:8. However, the risk for fetal infection is still substantial among pregnant women with late latent syphilis and low titers.[2,145] Concurrent syphilis infection has been associated with an increased risk of perinatal transmission of HIV to the infant.[146-152] No postpartum woman or neonate should leave the hospital without documentation of maternal syphilis serologic status determined at delivery. All women who have a fetal death after 20 weeks' gestation also should be tested for syphilis.

Screening

The American College of Obstetrics and Gynecologists recommends that serologic screening for syphilis using either the reverse or traditional testing algorithm should be conducted at the first prenatal visit and at 28 weeks' gestation and delivery.[153,154] In communities and populations in which

the prevalence of syphilis is high and in people at increased risk of infection (e.g., sex with multiple partners or new partner, sex in conjunction with drug use or transactional sex, late entry to or no prenatal care, methamphetamine or heroin use, hepatitis C infection, high alcohol use, incarceration, STI in pregnancy or a sexual partner with an STI, unstable housing or homelessness),[155,156] serologic testing may be performed more often.[2] Providers should ensure partners of those diagnosed with syphilis undergo testing and are treated according to stage. Screening for syphilis during pregnancy should be offered at sites providing episodic care, including emergency departments, jails, and prisons.[157,158] Several programs utilizing opt-out testing, with or without point-of-care testing for syphilis in nontraditional settings, have demonstrated improved detection and same-day treatment of syphilis during pregnancy.[159-161]

Diagnosis

Diagnostic considerations during pregnancy are the same as in those without HIV and are in alignment with the CDC STI Treatment Guidelines, as summarized below.

Signs and symptoms of syphilis do not differ during pregnancy. However, pregnancy-related rashes may complicate physical examination findings. Syphilis infection during pregnancy should be considered in individuals with reactive serology unless there is documentation of prior adequate treatment and a stage-appropriate decline in titers, either before or during pregnancy. If a treponemal EIA or CIA test is used for antepartum syphilis screening, all positive EIA or CIA tests should be followed with a quantitative nontreponemal test (RPR or VDRL), as titers are essential to monitoring treatment response. If the nontreponemal test is negative and the prozone reaction is ruled out (false-negative nontreponemal test that results from high antibody titer), then the results are discordant, in which case a second treponemal test (preferably the TP-PA) should be performed, preferably on the same specimen (see the Diagnosis section above).[53,162] If the second treponemal test is negative (e.g., EIA positive, RPR negative, and TP-PA negative), the positive EIA or CIA may represent a false-positive test result.[162,163] If there is a low risk for syphilis by history and low rates of syphilis in the community, no signs or symptoms of primary syphilis are present, the partner has no clinical or serologic evidence of syphilis, and follow-up with clinical care is likely, repeat serologic testing within 4 weeks can be considered to determine whether the EIA or CIA remains positive or whether the RPR, VDRL, or TP-PA result becomes positive. If both the RPR and TP-PA remain negative, no further treatment is necessary. If follow-up is not likely, treatment appropriate for the stage of syphilis is recommended with an isolated reactive treponemal test without a history of stage-appropriate syphilis treatment.

All neonates born to women with syphilis during pregnancy should be evaluated for congenital syphilis regardless of maternal treatment or response. Sonographic evaluation of fetuses exposed to syphilis can help inform providers about potential congenital infection and guide antenatal management.[2,164-166]

Treatment

Benzathine penicillin G is recommended for the treatment of syphilis during pregnancy and in settings of shortage should be prioritized for this population. Pregnant women should be treated with the recommended regimen for their clinical stage of disease **(AIII).** Penicillin is the only known effective antimicrobial for preventing transmission to the fetus and treating fetal infection; however, evidence is insufficient to determine the optimal penicillin regimen.[167,168] For the management of early syphilis during pregnancy, limited evidence indicates that a second dose of benzathine

penicillin G 2.4 million units IM administered 1 week after the single dose treatment may be of benefit for congenital syphilis prevention. However, one dose is considered adequate.[2,145,150,169,170] If a second dose of benzathine penicillin is administered, it should be provided no later than 9 days after the first dose.[2] For pregnant women with late latent syphilis, one dose of benzathine penicillin G 2.4 million units should be administered weekly for 3 weeks. If the interval between treatments exceeds 9 days, restarting the regimen is recommended **(BII).**[171] Sexual partners of pregnant women with syphilis should be evaluated and treated for syphilis according to stage of infection.

Treatment of syphilis during the second half of pregnancy may precipitate preterm labor or fetal distress if a Jarisch-Herxheimer reaction occurs.[172,173] Hepatomegaly, ascites, fetal hydrops, thickened placenta, and other sonographic signs of fetal or placental syphilis are associated with a greater risk of fetal treatment failure. Such cases should be managed in consultation with maternal fetal medicine specialists. Coordinated prenatal care and treatment are vital because providers should document that treatment is adequate for the syphilis stage and ensure that the clinical and nontreponemal responses are appropriate for the patient's disease stage.[2] Maternal serologic response during pregnancy after adequate therapy varies by stage of disease and timing of treatment.[174] If syphilis is diagnosed and treated before 24 weeks' gestation, serologic titers **should not be repeated** before 8 weeks after treatment but should be repeated at delivery. Titers should be repeated sooner if reinfection or treatment failure is suspected. A fourfold increase in nontreponemal titers during pregnancy should prompt evaluation and retreatment.[2] Most women will not achieve a fourfold decrease in titers before delivery; however, this does not indicate treatment failure. Inadequate antenatal treatment and incomplete congenital syphilis prevention is likely if delivery occurs within 30 days of therapy initiation, clinical signs of infection are present at delivery, or the maternal nontreponemal titer at delivery is fourfold higher than the pre-treatment titer.[2] There is no evidence that pregnant women with syphilis and HIV are at increased risk for delayed syphilis treatment response compared with women without HIV.[175]

Penicillin Allergy

Since no alternatives to penicillin have been proven effective and safe for the prevention of fetal infection, treatment with IM benzathine penicillin G remains the recommended treatment for syphilis during pregnancy **(AIII).** Penicillin skin testing and/or oral graded challenge might be helpful in identifying women at risk for acute allergic reactions **(BII).**[176] For those who have a history of more serious reactions, skin testing with oral challenge **is not recommended,** and pregnant women should undergo penicillin desensitization in the intensive care unit with appropriate referral services and fetal monitoring prior to and after the therapeutic dose is administered **(BII).**[176] Subsequent doses can be administered in the outpatient setting due to the prolonged half-life of IM benzathine penicillin G if administered within the recommended interval **(CIII).**[2,177,178]

Other Considerations

IM benzathine penicillin G remains the only recommended treatment for syphilis during pregnancy **(AIII).** If, in extreme circumstances, alternative regimens are considered, consultation with infectious diseases and maternal fetal medicine specialists and a nuanced patient–provider shared decision-making process is necessary **(BII).** Data are insufficient to recommend alternative non-penicillin options to treat primary, secondary, or latent syphilis in pregnancy; the appropriate duration and dosage are unknown.[179-181] Erythromycin and azithromycin **should not be used** because these regimens do not reliably cure maternal or fetal infection **(AII).**[167] Tetracyclines **are not generally**

recommended during pregnancy **(AII),**[150,182] although some data suggest concerns with this class of medications may not uniformly extend to doxycycline.[183]

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