

# Syphilis

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## Epidemiology

Syphilis, caused by *Treponema pallidum*, is associated with an increased risk of sexual acquisition and transmission of HIV.<sup>1-8</sup> In the United States, the national rate of primary and secondary syphilis has increased since 2001.<sup>9-12</sup> Although HIV infection, particularly in the advanced stages, may modify the diagnosis, natural history, or management of *T. pallidum* infection, the principles of syphilis management remain the same for people with and without HIV.<sup>13-18</sup>

## Clinical Manifestations

The effects of HIV on the protean manifestations of syphilis have been documented in multiple case reports and small case series, and in a limited number of large studies. In most people with HIV and syphilis, the clinical manifestations of syphilis are similar to those observed in people without HIV. Some studies suggest that infection with HIV may affect the clinical presentation of syphilis, as atypical or multiple genital lesions are more apparent, and accelerated progression of syphilis may be seen in people with advanced immunosuppression.<sup>16,17,19-22</sup> Primary or secondary syphilis also may cause a transient decrease in CD4 T lymphocyte (CD4) cell count and an increase in HIV viral load that improves with recommended syphilis treatment regimens.<sup>13,23-27</sup> Independent of HIV, previous syphilis can attenuate the clinical and laboratory manifestations of incident infection with *T. pallidum*.<sup>28-30</sup>

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, and primary lesions may be absent or missed in people with HIV.<sup>16,21,31</sup> 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. 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.<sup>13,17,18</sup> Mpox (formerly known as monkeypox) lesions can have a similar appearance and can occur simultaneously with early syphilis.<sup>32</sup> Condylomata lata (moist, flat papular lesions in warm intertriginous regions) can occur and may resemble condylomata acuminata caused by human papillomavirus. Lues maligna is a rare manifestation of secondary syphilis, characterized by papulopustular skin lesions that can evolve into ulcerative lesions with sharp borders and a dark central crust.<sup>33-35</sup> Manifestations of secondary syphilis involving other locations can occur (e.g., ocular and otic syphilis, meningoencephalitis, hepatitis, nephrotic syndrome, gastritis, pneumonia). In people with secondary syphilis, non-focal central nervous system (CNS) symptoms and cerebrospinal fluid (CSF) abnormalities, such as lymphocytic pleocytosis with a mildly elevated CSF protein, can occur.<sup>19,22,31,36-40</sup> Signs and symptoms of primary and secondary syphilis can overlap or persist from a few days to several weeks before resolving. In some instances, recrudescence of symptoms may occur after secondary infection with subsequent evolution to latent stages.

Latent syphilis is defined as serologic reactivity without clinical signs and symptoms of infection. Latent syphilis can be categorized as early latent syphilis if  $\leq 1$  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. Tertiary syphilis refers to gumma, cardiovascular syphilis, psychiatric manifestations (e.g., memory loss, personality changes), or late neurosyphilis that can develop 10 to 30 years after untreated infection.

Neurosyphilis, similar to ocular and otic syphilis, can occur at any stage of syphilis with different clinical presentations, including 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 concomitant ocular syphilis (including uveitis) or meningitis, may be more common in people with HIV.<sup>19,22,40-46</sup>

Syphilitic uveitis or other ocular syphilis manifestations (e.g., neuroretinitis and 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.<sup>47</sup>

All people with ocular symptoms and reactive syphilis serology 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 serology, and confirmed ocular abnormalities on examination, CSF examination is unnecessary before treatment. CSF analysis might be helpful in evaluating people with ocular symptoms and reactive syphilis serology 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. Ocular syphilis should be treated similarly to neurosyphilis, even if a CSF examination is normal.

Isolated hearing loss or other otologic symptoms can occur at any stage of syphilis or can be associated with neurosyphilis. Among people with isolated auditory abnormalities and reactive syphilis serology, CSF evaluation is likely to be normal and is not necessary before treatment.<sup>48</sup>

## Diagnosis

### ***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 early syphilis.<sup>49</sup> Although *T. pallidum* direct antigen detection tests are no longer commercially available, some laboratories provide locally developed and validated polymerase chain reaction (PCR) tests for the direct detection of *T. pallidum*.

### ***Serologic Testing***

Serologic diagnosis of syphilis traditionally has involved screening for nontreponemal antibodies with confirmation of reactive tests by treponemal-based assays.<sup>13,50,51</sup> A serologic diagnosis of syphilis is based on nontreponemal tests (i.e., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]), followed by confirmation with treponemal tests (i.e., *T. pallidum* particle agglutination [TP-PA], enzyme immunoassays [EIAs], chemiluminescence

immunoassays [CIAs], fluorescent treponemal antibody absorbed [FTA-ABS], or immunoblots). Rapid treponemal assays are also available to screen for syphilis; however, these tests can not differentiate recent or past infection, so testing with a nontreponemal test is indicated to inform further patient management.<sup>50-52</sup> Use of only one type of serologic test (nontreponemal or treponemal) is insufficient for diagnosis and can result in false-negative results among people tested during primary syphilis and false-positive results among people without syphilis or previously treated syphilis.

### ***Traditional Algorithm***

False-positive nontreponemal test results can be associated with medical conditions and other factors unrelated to syphilis, including HIV, autoimmune disease, vaccinations, injection drug use, pregnancy, and older age.<sup>50</sup> Individuals with a reactive nontreponemal test should always receive a treponemal test to confirm the syphilis diagnosis. Nontreponemal test antibody titers can correlate with disease activity and are used for monitoring treatment response. Sequential serologic tests should be performed using the same testing method (VDRL or RPR), preferably by the same laboratory. VDRL and RPR are equally valid assays; however, quantitative results from the two tests cannot be compared directly with each other because the methods are different, and RPR titers frequently are slightly higher than VDRL titers.

Nontreponemal test titers usually decrease after treatment and can become nonreactive with time. However, in some instances nontreponemal antibodies might decrease less than fourfold after treatment (i.e., inadequate serologic response) or might decline appropriately but fail to serorevert and persist for a long period. Atypical nontreponemal serologic test results (e.g., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV status. When serologic tests do not correspond with clinical findings indicative of primary, secondary, or latent syphilis, presumptive treatment is recommended for people with risk factors for syphilis, and use of other tests (e.g., biopsy for histology and immunostaining and PCR of lesion) should be considered. For most people with HIV, serologic tests are accurate and reliable for diagnosing syphilis and evaluating response to treatment.<sup>28</sup>

### ***Reverse-Sequence Algorithm***

Most people who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of adequate treatment or disease activity and do not predict treatment response.

Some laboratories have initiated a reverse-sequence screening algorithm using treponemal EIA or CIA as a screening test, followed by a reflex-quantitative nontreponemal test if the EIA or CIA is positive.

This reverse-sequence algorithm can identify people previously treated for syphilis, those with untreated or incompletely treated syphilis, and those with false-positive results that can occur with a low likelihood of infection.<sup>13,53</sup> People with a positive treponemal screening test should have a standard quantitative nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions.

In the reverse-sequence screening strategy, having a positive treponemal EIA or CIA and a negative reflex-quantitative nontreponemal test requires a second treponemal test (based on different antigens from the initial test) to confirm the results of the positive initial treponemal test. If a second

treponemal test is positive, people who have been treated appropriately for their stage of syphilis will require no further treatment unless sexual risk history suggests likelihood of re-exposure or there is a sustained fourfold increase in nontreponemal antibody titers. In this instance, a repeat nontreponemal test 2 to 4 weeks after the most recent possible exposure is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection (e.g., early-stage syphilis), previously untreated people should be treated for late latent syphilis. If the second treponemal test is negative and the risk of syphilis is low, no treatment is indicated.<sup>13,54</sup> However, if the risk of syphilis is high, treatment should be considered. Multiple studies demonstrate that high quantitative index values or high signal-to-cutoff ratio from treponemal EIA or CIA tests correlate with TP-PA positivity, which might eliminate the need for additional confirmatory testing; however, the range of index values varies among different treponemal immunoassays, and the values that correspond to high levels of reactivity with confirmatory testing might differ by immunoassay.<sup>51,55,56</sup>

In the absence of neurologic signs or symptoms, risk of neurosyphilis is low in people with a reactive treponemal test and a nonreactive nontreponemal test<sup>55,57</sup>; examination of CSF is not recommended.

Early-stage disease (i.e., primary, secondary, and early latent syphilis) is identified using the same diagnostic tests used in people without HIV: standard serologic tests and darkfield microscopy of mucocutaneous lesions, if available. VDRL and RPR titers may be higher, lower (in rare instances), or delayed in people with HIV with early-stage syphilis.<sup>58-62</sup> No data indicate that treponemal tests perform differently among people with HIV<sup>51</sup>; although uncommon, false-negative serologic tests for syphilis can occur with documented *T. pallidum* infection.<sup>61,62</sup> When serologic tests do not correspond with clinical findings indicative of primary or secondary syphilis, presumptive treatment is recommended for people with risk factors for syphilis, and dilution of the sample for prozone phenomenon should be considered. For most people with HIV, serologic tests are accurate and reliable for diagnosing syphilis and for determining response to treatment.

By definition, people with latent syphilis have serological evidence of syphilis (nontreponemal and treponemal testing) 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 is defined by evidence of infection during the preceding year—

- A documented seroconversion or 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.<sup>13</sup>

Late latent syphilis is defined as syphilis in a person who does not have evidence of acquiring infection in the preceding year.

All people with syphilis and signs or symptoms suggesting neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke, altered mental status) warrant evaluation for neurosyphilis.

CSF abnormalities (i.e., elevated protein and mononuclear pleocytosis) are common in early-stage syphilis<sup>36</sup> and in people with HIV, even 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  $\leq 350$  cells/mm<sup>3</sup> or in combination with RPR titers  $\geq 1:32$ .<sup>39,40,63,64</sup> However, unless neurologic signs and 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. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count, CSF protein, and CSF-VDRL) in the setting of reactive serologic test results and neurologic signs and symptoms. CSF examination may indicate mononuclear pleocytosis (6–200 cells/mm<sup>3</sup>), mildly elevated protein concentration, or a reactive CSF-VDRL. Among people with HIV, the CSF leukocyte count can be elevated (>5 white blood cell count [WBC]/mm<sup>3</sup>); using a higher cutoff (>20 WBC/mm<sup>3</sup>) may improve the specificity of neurosyphilis diagnosis.<sup>39</sup> In people with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not contaminated with blood) is considered diagnostic of neurosyphilis; however, it is thought to have a very low sensitivity and therefore may miss true disease. Therefore, in people with neurologic signs or symptoms, reactive serologic test results, lymphocytic pleocytosis, or elevated protein, neurosyphilis should be considered even when the CSF-VDRL is negative. In that instance, additional evaluation by using FTA-ABS or TP-PA testing on CSF might be warranted.<sup>13</sup> The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Fewer data are available regarding CSF TP-PA; however, the sensitivity and specificity appears similar to the CSF FTA-ABS.<sup>65,66</sup> Neurosyphilis is highly unlikely with a negative CSF FTA-ABS or TP-PA test, especially among people with nonspecific neurologic signs and symptoms.

RPR tests of the CSF have been associated with a high false-negative rate and are not recommended.<sup>67</sup> PCR-based diagnostic methods are not currently recommended as diagnostic tests for neurosyphilis.

## Preventing Disease

### Recommendations for Preventing Syphilis

Management of Sexual Partners After Exposure to <i>Treponema pallidum</i> (Syphilis) to Prevent Disease
<p><b>Indication for Treatment</b></p> <ul style="list-style-type: none"> <li>• Individuals exposed sexually within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner regardless of syphilis serologic status (<b>AII</b>)</li> <li>• Individuals exposed &gt;90 days before syphilis diagnosis in a sex partner, if syphilis serologic test results are not available immediately and the opportunity for follow-up is uncertain (<b>AIII</b>)</li> </ul> <p><b>Treatment</b></p> <ul style="list-style-type: none"> <li>• See therapy for early-stage syphilis in the Recommendations for Treating Syphilis table.</li> </ul>

**Note:** Additional logistical information is available from the Centers for Disease Control and Prevention at <https://www.cdc.gov/std/treatment/drug-notice.htm>.

The resurgence of syphilis and other sexually transmitted infections (STIs), as well as the emergence of mpox, in men who have sex with men (MSM) with HIV underscores the importance of primary prevention of syphilis in this population, 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.<sup>13,68-72</sup> 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 who have multiple or anonymous partners.<sup>13,73-75</sup> The occurrence of syphilis or any other STI in a person with HIV is an indication of risk 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.<sup>76,77</sup> People undergoing screening or treatment for syphilis also should be evaluated for other STIs, including mpox, chlamydia, and gonorrhea at anatomic sites of exposure in men and chlamydia, gonorrhea, and trichomonas infections in women.<sup>13,78</sup>

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. 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; empiric treatment of sexual partners exposed to syphilis will prevent the development of disease and onward syphilis transmission.<sup>79-82</sup> Individuals with recent sexual contact with a person with syphilis in any stage should be evaluated clinically and serologically and treated presumptively. People who have had sexual contact with an individual diagnosed with primary, secondary, or early latent syphilis during the 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative (**AII**).

People who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the 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.<sup>13</sup> 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) 3 months plus the duration of symptoms for people who receive a diagnosis of primary syphilis, (2) 6 months plus the duration of symptoms for those diagnosed with secondary syphilis, and (3) 1 year for people diagnosed with early latent syphilis.

### ***Pre-Exposure Prophylaxis and Post-Exposure Prophylaxis for Prevention***

Doxycycline pre-exposure prophylaxis (PrEP) has been examined for prevention of bacterial STIs. In a pilot study, 30 MSM with HIV with previous syphilis were randomly assigned to doxycycline 100 mg daily for 48 weeks versus a financial incentive-based behavioral intervention; doxycycline was associated with a lower incidence of syphilis, but this did not reach statistical significance due to small sample size.<sup>83</sup>

Post-exposure prophylaxis (doxycycline 200 mg after unprotected anal sex) has been studied among MSM and transgender women, with a reduction in incident syphilis by 73%.<sup>84</sup> Several recent randomized open-label clinical trials have found that doxycycline 200 mg after condomless sex among MSM or transgender women with HIV or on HIV PrEP significantly reduced chlamydia, gonorrhea, and syphilis acquisition; a randomized trial of cisgender women on HIV PrEP administered doxycycline 200 mg within 72 hours after sex did not reduce chlamydia, gonorrhea, or syphilis acquisition.<sup>85</sup> There is ongoing evaluation regarding the potential impact of STI postexposure prophylaxis on antimicrobial resistance and the microbiome. Other studies are underway or in development regarding doxycycline prophylaxis for bacterial STIs.<sup>86,87</sup>

Targeted mass treatment of high-risk populations with azithromycin has not been demonstrated to be effective.<sup>88</sup> Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in people with HIV and reports of chromosomal mutations associated with macrolide-resistant *T. pallidum*.<sup>89-93</sup>

## Treatment

### Recommendations for Treating Syphilis

General Considerations for Treating Syphilis
<ul style="list-style-type: none"> <li>• Selection of the appropriate penicillin preparation is important because <i>T. pallidum</i> can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by certain forms of penicillin.</li> <li>• Combinations of oral benzathine penicillin and procaine penicillin or short-acting benzathine-procaine penicillin (Bicillin C-R) preparations are not appropriate for syphilis treatment.</li> <li>• 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.</li> <li>• 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.</li> </ul>
Treating <i>Treponema pallidum</i> Infections (Syphilis) Depending on Stage of Disease
<p><b>Primary, Secondary, and Early Latent Syphilis [≤1 year]</b></p> <p><i>Recommended Therapy</i></p> <ul style="list-style-type: none"> <li>• Benzathine penicillin G 2.4 million units IM in a single dose <b>(AII)</b><sup>a</sup></li> </ul> <p><i>Alternative Therapy (For Penicillin-Allergic Patients; See Note Below)</i></p> <ul style="list-style-type: none"> <li>• Doxycycline 100 mg PO twice daily for 14 days <b>(BII)</b>,<sup>b</sup> or</li> <li>• Ceftriaxone 1 g IM or IV daily for 10–14 days <b>(BII)</b><sup>b</sup></li> </ul> <p><b>Note:</b> People with penicillin allergy whose compliance or follow-up cannot be ensured and who have syphilis during pregnancy should undergo penicillin desensitization and treatment with benzathine penicillin.</p> <p>For management of early syphilis during pregnancy, limited evidence indicates a second dose of benzathine penicillin G 2.4 million units IM 1 week after the single dose treatment may be of benefit for congenital syphilis prevention <b>(BII)</b>.</p> <p><b>Late Latent (&gt;1 year) or Latent of Unknown Duration</b></p> <p><i>Recommended Therapy</i></p> <ul style="list-style-type: none"> <li>• Benzathine penicillin G 2.4 million units IM weekly for three doses <b>(AII)</b><sup>a</sup></li> </ul> <p><i>Alternative Therapy (For Penicillin-Allergic Patients)</i></p> <ul style="list-style-type: none"> <li>• Doxycycline 100 mg PO twice daily for 28 days <b>(BIII)</b></li> </ul> <p><b>Note:</b> People with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin <b>(AII)</b>.</p>



## Recommendations for Preventing and Treating Syphilis

### Tertiary—Cardiovascular or Gummatous Disease

- Perform CSF examination and obtain infectious diseases consultation to guide management.
- People with CSF abnormalities should be treated with a regimen for neurosyphilis **(AII)**.

#### *Recommended Therapy*

- Benzathine penicillin G 2.4 million units IM weekly for three doses for people without neurosyphilis **(AII)**<sup>a</sup>

### Neurosyphilis, Otic, or Ocular Syphilis

#### *Recommended 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)**, *with or without*
- Benzathine penicillin G 2.4 million units IM x 1 after completion of aqueous crystalline penicillin G infusion **(CIII)**<sup>a</sup>

#### *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)**. Procaine penicillin has been discontinued by the manufacturer as of June 13, 2023 (see [FDA Drug Shortages](#)).

**Note:** People who are allergic to sulfa-containing medications **should not** be given probenecid; thus, the procaine penicillin regimen is **not recommended (AIII)**.

### For Penicillin-Allergic Patients with Neurosyphilis, Otic, or Ocular Syphilis

#### *Recommended Therapy*

- Desensitization to penicillin

#### *Alternative Therapy (If Desensitization Is Not Feasible and Not Pregnant)*

- Ceftriaxone 2 g IV daily for 10–14 days **(BII)**

**Note:** People who have a history of IgE-mediated penicillin hypersensitivity may lose their sensitivity after 10 years, and a subsequent negative skin test evaluation followed by oral challenge can be considered. 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 is the preferred approach.

<sup>a</sup> Benzathine penicillin is currently on the FDA drug shortage webpage due to limited supply. Updates on the expected duration for the shortage are available on the [FDA Drug Shortage webpage](#).

<sup>b</sup> Skin testing for penicillin allergy can be useful in circumstances in which the reagents and expertise are available.

**Note:** Additional logistical information is available from the Centers for Disease Control and Prevention at <https://www.cdc.gov/std/treatment/drug-notice.htm>.

**Key:** CNS = central nervous system; CSF = cerebrospinal fluid; FDA = U.S. Food and Drug Administration; IgE = immunoglobulin E; IM = intramuscular; IV = intravenously; PO = orally

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 (within the previous 12 months).<sup>13,59,94,95</sup> However, in people with HIV, more frequent clinical and serologic evaluation is recommended—at least every 3 months rather than every 6 months—because serologic nonresponse and neurologic complications may be more frequent.<sup>19,96,97</sup> Use of antiretroviral therapy (ART) in people with syphilis has also been associated with a reduced risk of serologic failure of syphilis treatment<sup>22</sup> and a lower risk of developing neurosyphilis.<sup>22</sup>



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**).<sup>13</sup> High-dose amoxicillin given with probenecid in addition to benzathine penicillin G in early syphilis is not associated with improved clinical outcomes.<sup>59</sup> People with a penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G (**AIII**).

The efficacy of alternative non-penicillin regimens in people with HIV and early syphilis has not been well studied. The use of any alternative penicillin treatment regimen should be undertaken only with close clinical and serologic monitoring. The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (the Panel) supports the use of doxycycline, 100 mg orally twice daily for 14 days, to treat early syphilis (**BII**).<sup>98,99</sup> Based on limited clinical studies in people with and without HIV, ceftriaxone (1 g daily either IM or intravenously [IV] for 10–14 days) is also recommended for treating early-stage syphilis (**BII**), but the optimal dose and duration of therapy have not been defined.<sup>100–102</sup> There are limited data suggesting a single 2-g oral dose of oral azithromycin can be effective for treating early syphilis<sup>103–105</sup>; however, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been reported most commonly in MSM.<sup>89–93,106</sup> Azithromycin has not been well studied in people with HIV or among pregnant people. Therefore, azithromycin should not be used as treatment for syphilis (**AII**).

In people with HIV who have late latent syphilis, treatment with three weekly IM injections of 2.4 million units of benzathine penicillin G is recommended (**AII**). Alternative therapy is doxycycline, 100 mg orally twice daily for 28 days; however, it has not been sufficiently evaluated in people with HIV (**BIII**). 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.<sup>107,108</sup> If the clinical situation requires use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

People with HIV who have clinical evidence of tertiary syphilis (cardiovascular or gummatous disease) should have CSF examination to rule out CSF abnormalities before therapy is initiated. 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**).<sup>13</sup> However, due to the complexity of tertiary syphilis management, especially cardiovascular syphilis, health care providers are advised to consult an infectious disease specialist.

People with HIV diagnosed with neurosyphilis or ocular or otic syphilis should receive IV aqueous crystalline penicillin G, 18 to 24 million units daily, administered 3 to 4 million units IV every 4 hours or by continuous infusion for 10 to 14 days (**AII**), or procaine penicillin, 2.4 million units IM once daily plus probenecid 500 mg orally four times a day for 10 to 14 days (**BII**).<sup>13</sup> However, procaine penicillin has been recently discontinued by the manufacturer.<sup>109</sup>

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, such therapy has not been proven beneficial.

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 can be considered to provide a comparable duration of therapy (**CIII**).<sup>13</sup>

People who have a history of immunoglobulin E mediated penicillin hypersensitivity may lose their sensitivity after 10 years,<sup>110,111</sup> and a subsequent negative skin test evaluation followed by oral challenge can be considered. 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 is the preferred approach. However, based on limited data, ceftriaxone (2 g daily IV for 10–14 days) is recommended as an acceptable alternative regimen (**BII**).<sup>100,101,108</sup> Other alternative regimens for neurosyphilis have not been evaluated adequately. Syphilis treatment recommendations are available in the [2021 Centers for Disease Control and Prevention STI Treatment Guidelines](#).<sup>13</sup>

### ***Special Considerations with Regard to Starting Antiretroviral Therapy***

There are no special considerations regarding the initiation of ART in patients with 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.<sup>112,113</sup>

### ***Monitoring and Adverse Events***

Clinical and serologic responses (fourfold decrease from the nontreponemal titer at the time of treatment) to treatment of early-stage (primary, secondary, and early latent) disease should be performed at 3, 6, 9, 12, and 24 months after therapy to ensure resolution of signs and symptoms within 3 to 6 months and seroreversion or a fourfold decline in nontreponemal titers within 24 months. Clinical and serologic responses to treatment are similar in people with HIV; subtle variations can occur, however, including a slower temporal pattern of serologic response in people with HIV.<sup>13,59,79,94,95</sup> Factors associated with the serologic response to treatment in people without HIV include younger age, earlier syphilis stage, and higher RPR titer.<sup>114–116</sup> 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 of greater than 2 weeks, treatment failure or reinfection should be considered and managed per recommendations (see [Managing Possible Treatment Failure or Reinfection](#)). The potential for reinfection should be based on the sexual history and risk assessment. Clinical trial data have demonstrated that 15% 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.<sup>13,59</sup> Serum nontreponemal test titers may remain reactive, usually  $\leq 1:8$ , although can be higher, for prolonged periods. In addition, people treated for early-stage syphilis who have a fourfold decline in titer may not serorevert to a negative nontreponemal test, which does not represent treatment failure but an inadequate serologic response.<sup>117</sup>

Response to therapy for late 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, if initially high ( $\geq 1:32$ ), within 24 months of therapy. However, data to define the precise time intervals for adequate serologic responses are limited. Many people with low titers 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](#)). The potential for reinfection should be based on sexual history and risk assessment.<sup>13</sup>

The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. 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.<sup>22,39</sup> Among people with HIV who are on effective ART and people without HIV, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment.<sup>118,119</sup> Therefore, repeated CSF examinations are unnecessary for people without HIV or among people with HIV who are on ART and who exhibit serologic and clinical responses to treatment.<sup>13</sup>

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.<sup>120</sup> 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.

## Managing Possible Treatment Failure or Reinfection

Retreatment should be considered for people with early-stage syphilis who have persistent or recurring clinical signs or symptoms of disease, or a sustained fourfold increase in serum nontreponemal titers after an initial fourfold decrease following treatment. The assessment for potential reinfection should be informed by a sexual history and syphilis risk assessment including information about a recent sexual partner with signs or symptoms or recent treatment for syphilis. People who have had syphilis are at increased risk for reinfection. One study showed that 6% of MSM had a repeat early-stage syphilis infection within 2 years of initial infection; HIV infection and multiple sexual partners were associated with increased risk of reinfection.<sup>11</sup> Serologic response should be compared to the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, as definitive criteria for cure or failure have not been well established. 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.<sup>13,38,97</sup>

People who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur, or a fourfold increase or greater in titer sustained for more than 2 weeks) and who are at low risk for reinfection should be managed for possible treatment failure. If neurologic symptoms or signs are identified, a CSF evaluation is recommended, with findings guiding management. People with nontreponemal titers that do not decrease fourfold within 12 to 24 months of therapy should also be managed as a possible treatment failure. Management should include neurologic examination and retreatment with benzathine penicillin G, 2.4 million units at 1-week intervals for 3 weeks (**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. The Panel supports 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 in people with recurrent signs and symptoms of primary or secondary syphilis or a fourfold increase in nontreponemal titers within the past year who are at high risk of syphilis reinfection (**CIII**).

People treated for late latent syphilis should have a CSF examination and be re-treated 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; this can also be considered if they experience an inadequate serologic response (i.e., less than fourfold decline in an initially high [ $\geq 1:32$ ] nontreponemal test titer) within 12 months for early syphilis and 24 months for late latent

syphilis. If CSF examination is consistent with CNS involvement, retreatment should follow the recommendations for treatment of neurosyphilis. People with a normal CSF examination or without ocular or otic symptoms should be treated with benzathine penicillin 2.4 million units IM weekly for three doses (**BIII**). The Panel supports 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 in people with signs or symptoms of primary or secondary syphilis or a fourfold increase in nontreponemal titers within the past year who are at high risk of reinfection (**CIII**).

Among people with HIV who are on effective ART and people without HIV, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment.<sup>118,119</sup> Therefore, repeated CSF examinations are unnecessary for people with HIV who are on ART and who exhibit serologic and clinical responses after treatment.

## Special Considerations During Pregnancy

In recent years, there has been a resurgence in neonatal syphilis in the United States. Syphilis in pregnancy is associated with increased risk of several adverse outcomes, including pregnancy loss, preterm birth, stillbirth, impaired fetal growth, neonatal mortality, and congenital infection, which can cause abnormalities in multiple organ systems. The clinical manifestations of syphilis in pregnancy are similar in people with and without HIV.

Serologic screening for syphilis should be conducted at the first prenatal visit and at 28 weeks. In communities and populations in which the prevalence of syphilis is high and in people at increased risk of infection (i.e., sex with multiple partners or new partner, sex in conjunction with drug use or transactional sex, late entry or no prenatal care, methamphetamine or heroin use, hepatitis C, alcohol misuse,<sup>121</sup> incarceration, STI in pregnancy or partner with STI, unstable housing or homelessness),<sup>122</sup> serologic testing should also be performed at delivery.<sup>13</sup> Providers should consider offering screening for syphilis to sexual partners of pregnant people.

Screening for syphilis during pregnancy should be offered at sites providing episodic care, including emergency departments, jails, and prisons.<sup>123</sup> Antepartum screening with nontreponemal testing is typical, but treponemal screening is being used in some settings. If a treponemal EIA or CIA test is used for antepartum syphilis screening, all positive EIA or CIA tests should be confirmed 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; a second treponemal test should be performed, preferably on the same specimen (see Diagnosis section above).<sup>124</sup> If the second treponemal test is negative (i.e., EIA positive, RPR negative, and TP-PA negative), the positive EIA or CIA is more likely to represent a false-positive test result for people who are living in communities with low rates of syphilis, have a partner who is uninfected, and have no history of treated syphilis.<sup>55,124</sup> During pregnancy, if there is a low risk for syphilis, there are no signs or symptoms of primary syphilis, the partner has no clinical or serologic evidence of syphilis, and the pregnant person is likely to follow up with clinical care, 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 for people with an isolated reactive treponemal test without a history of syphilis treatment.

No postpartum individual or neonate should leave the hospital without documentation of maternal syphilis serologic status determined at least once during pregnancy.<sup>13</sup> All individuals who have a fetal death after 20 weeks of gestation also should be tested for syphilis.

Rates of transmission to the fetus and adverse pregnancy outcomes for untreated syphilis are highest with primary, secondary, and early latent syphilis and decrease with increasing duration of infection. Pregnancy does not appear to alter the clinical course, manifestations, or diagnostic test results for syphilis infection in adults. Concurrent syphilis infection has been associated with increased risk of perinatal transmission of HIV to the infant.<sup>125-131</sup>

Syphilis infection during pregnancy should be considered in those with reactive syphilis serology unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined appropriately for the stage of syphilis. In general, the risk of antepartum fetal infection or congenital syphilis at delivery is related to the quantitative maternal nontreponemal titer, especially if  $\geq 1:8$ . However, risk for fetal infection is still substantial among pregnant people with late latent syphilis and low titers. All neonates born to people with syphilis should be evaluated for congenital syphilis regardless of maternal treatment or response.

Sustained low nontreponemal titers after documented treatment for the appropriate stage of infection might not require additional treatment; however, rising or persistently high antibody titers may indicate reinfection or treatment failure, and retreatment should be considered.<sup>13</sup>

Benzathine penicillin G is recommended for the treatment of syphilis during pregnancy. Penicillin is the only known effective antimicrobial for preventing transmission to the fetus and for treatment of fetal infection; however, evidence is insufficient to determine the optimal penicillin regimen.<sup>132</sup> For management of early syphilis during pregnancy, limited evidence indicates that a second dose of benzathine penicillin G 2.4 million units IM 1 week after the single dose treatment may be of benefit for congenital syphilis prevention.<sup>13,129,133-135</sup> If a second dose of benzathine penicillin is administered, it should be provided no later than 9 days after the first dose.<sup>13</sup> Sexual partners of pregnant individuals with syphilis should be referred for evaluation and treatment.

Since no alternatives to penicillin have been proven effective and safe for prevention of fetal infection, desensitization and treatment with penicillin should be performed in pregnancy for those who have a history of penicillin allergy (**AIII**).<sup>13</sup> Erythromycin and azithromycin should not be used because these regimens do not reliably cure infection in the pregnant individual or the fetus (**AII**).<sup>132</sup>; tetracyclines should be avoided in the second and third trimesters of pregnancy (**AII**).<sup>129,136</sup> Data are insufficient to recommend ceftriaxone<sup>137,138</sup> for treatment of antenatal infection and prevention of congenital syphilis (**BIII**).

Treatment of syphilis during the second half of pregnancy may precipitate preterm labor or fetal distress if a Jarisch-Herxheimer reaction occurs.<sup>139,140</sup> Obstetric attention is advised if contractions develop or a decrease in fetal movement is noted after treatment. During the second half of pregnancy, syphilis management can be facilitated with sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (e.g., hepatomegaly, ascites, fetal hydrops, thickened placenta) indicate a greater risk of fetal treatment failure.<sup>141</sup> Such cases should be managed in consultation with high-risk obstetric specialists. After 20 weeks of gestation, fetal and contraction monitoring for 24 hours after initiation of treatment for early syphilis should be considered when sonographic findings indicate fetal infection.

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 antibody responses are appropriate for the patient's disease stage. Maternal serologic response during pregnancy after adequate therapy varies by stage of disease and timing of treatment.<sup>142</sup> If syphilis is diagnosed and treated at or before 24 weeks' gestation, serologic titers should not be repeated before 8 weeks after treatment but should be repeated again at delivery. Titers should be repeated sooner if reinfection or treatment failure is suspected. For syphilis diagnosed and treated after 24 weeks' gestation, serologic titers should be repeated at delivery.<sup>13</sup> A majority of women will not achieve a fourfold decrease in titers before delivery, although this does not indicate treatment failure. Inadequate antenatal treatment is likely if delivery occurs within 30 days of therapy, clinical signs of infection are present at delivery, or the maternal nontreponemal titer at delivery is fourfold higher than the pre-treatment titer. 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.<sup>143</sup>

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