Management of Syphilis in Patients with HIV

Sexually Transmitted Infections Guidelines Committee, February 2018

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Purpose of This Guideline

This guideline on treatment of syphilis in adult patients with HIV was developed by the New York State Department of Health (NYSDOH) AIDS Institute (AI) to guide primary care providers and other practitioners in New York State in treating patients with HIV and syphilis coinfection. Accordingly, this guideline addresses the following topics in the management of syphilis: transmission and prevention, screening, diagnosis, reporting, treatment, and post-treatment monitoring. This guideline aims to achieve the following goals:

- Increase the number of New York State residents with HIV and syphilis coinfection who are identified and treated with effective interventions.
- Support the NYSDOH Prevention Agenda 2013-2018 to reduce the case rate of primary and secondary syphilis by 10% to no more than 10.1 cases per 100,000 men and 0.4 cases per 100,000 women and reduce disparities for specific populations that are disproportionately affected by syphilis infection [NYSDOH 2010, 2015].
- Reduce the growing burden of morbidity and mortality associated with syphilis infection.
- Integrate current evidence-based clinical recommendations into the healthcare-related implementation strategies of the Ending the Epidemic initiative, which seeks to end the AIDS epidemic in New York State by the end of 2020.

The Burden of Syphilis Infection

Syphilis, a systemic infection caused by the bacterium Treponema pallidum, is the third most frequently reported sexually transmitted infection (STI) in the United States behind chlamydia and gonorrhea [CDC 2017b]. Syphilis and other ulcer-producing STIs are risk factors for acquiring or transmitting HIV infection because they directly increase the likelihood that genital secretions will contain an infectious amount of HIV-1 [CDC 2016]. In addition, syphilis infection might indicate ongoing sexual behaviors that place a person at increased risk of acquiring or transmitting HIV infection [Pathela, et al. 2015].

Since 2001, rates of primary and secondary syphilis—the most infectious stages of the disease—have increased annually in the United States [CDC 2017b], especially among HIV-infected men who have sex with men (MSM) [CDC 2002, 2017b]. In 2016, case counts and rates of primary and secondary syphilis were the highest recorded nationally since 1994 at 27,814 and 8.7 cases per 100,000, respectively [CDC 2017b]. Men, who accounted for almost 90% of new primary and secondary syphilis cases in 2016, are disproportionately affected. MSM accounted for 58.1% of all primary and secondary syphilis cases overall, and 47% of MSM with syphilis reportedly had HIV [CDC 2017b]. The rate of reported primary and secondary syphilis cases in women increased by 35.7% to 3,049 cases during 2015-2016, and the rate of congenital syphilis increased by 27.6% to 628 cases.

New York ranks fifth among the 50 states in rates of primary and secondary syphilis, with 2,455 cases reported in 2016 [CDC 2017b].

<table>
<thead>
<tr>
<th>New York State (including New York City)</th>
<th>Nationwide</th>
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<tr>
<td>• 7,795 cases (all stages) reported in 2016</td>
<td>• 88,042 cases (all stages) reported in 2016</td>
</tr>
<tr>
<td>− 2,455 primary and secondary cases, an increase of 18.3% from 2015</td>
<td>− 27,814 primary and secondary cases reported, an increase of 17.6% from 2015</td>
</tr>
<tr>
<td>− 13 congenital cases, a 7.7% increase from 2015</td>
<td>− 628 cases of congenital cases, an increase of 27.6% from 2015</td>
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</tbody>
</table>
Long-term infection can affect multiple organ systems, including the brain, nerves, eyes, heart, blood vessels, liver, bones, and joints [CDC 2017c], and can cause visual impairment, stroke [CDC 2016], or death. Up to 40% of cases of untreated syphilis in pregnant women results in infant death. Infants who survive can have cataracts, deafness, or seizures.

STIs pose individual, social, and financial burdens and lead to costly health complications, including those affecting reproductive health, fetal and perinatal health, and transmission of HIV infection [ODPHP 2017]. Data suggest that the annual, direct cost of treating STIs in the United States is $15.6 billion, with HIV infection accounting for $12.6 billion and syphilis $39.3 million [Owusu-Edusei, et al. 2013].

The Role of Primary Care Providers in New York State

The goal of this guideline is to aid primary care providers and other clinicians in New York State in diagnosing and treating syphilis infection in adult patients with HIV. Primary care providers are often the first to see patients with STI symptoms. Nurses in New York State are authorized to execute non-patient specific orders and protocols (ordered by a physician or nurse practitioner) for administering HIV testing and medically screening at-risk persons for syphilis, chlamydia and/or gonorrhea. As such, primary care providers and other clinicians assume a major role in the diagnosis and treatment of patients with HIV and STIs and in counseling patients to avoid or prevent high-risk behaviors that might lead to STIs.

The NYSDOH AI STI Committee has developed a set of measures designed to assess providers’ quality of STI care and treatment and identify areas for improvement, with the goal of reversing the rising rate of STI transmissions and recognizing sexual health as a primary care priority.

Development of This Guideline

This guideline was developed by the NYSDOH AI Clinical Guidelines Program, which is a collaborative effort between the NYSDOH AI Office of the Medical Director and the Johns Hopkins University School of Medicine, Division of Infectious Diseases.

Established in 1986, the goal of the Clinical Guidelines Program is to develop and disseminate evidence-based, state-of-the-art clinical practice guidelines to improve the quality of care provided to people with HIV, hepatitis C virus, and STIs and to improve drug user health and LGBT health throughout the State of New York. NYSDOH AI guidelines are developed by committees of clinical experts through a consensus-driven process.

The NYSDOH AI charged the Sexually Transmitted Infections Guidelines Committee with developing evidence-based clinical recommendations for primary care clinicians in New York State who treat patients with syphilis infection. The resulting recommendations are based on an extensive review of the medical literature and reflect consensus among this panel of STI experts. Each recommendation is rated for strength and for quality of the evidence (see below). If recommendations are based on expert opinion, the rationale for the opinion is included.

<table>
<thead>
<tr>
<th>AIDS Institute HIV Clinical Guidelines Program Recommendations Rating Scheme</th>
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<tbody>
<tr>
<td><strong>Strength of Recommendation</strong></td>
</tr>
<tr>
<td>A = Strong</td>
</tr>
<tr>
<td>B = Moderate</td>
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<tr>
<td>C = Optional</td>
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</table>
Transmission and Prevention

RECOMMENDATIONS

Transmission and Prevention

- Clinicians should inform patients with HIV about the risk of acquiring syphilis and other sexually transmitted infections (STIs) from close physical contact with all sites of possible exposure, including the anus, cervix, vagina, urethra, tongue, oropharynx, or any other location where infectious lesions may be present. (A3)

Patient Education

- When patients with HIV are diagnosed with early syphilis (primary, secondary, or early latent stage), clinicians should educate patients about the following:
  - Risk-reduction strategies, including the value of condom use (A2)
  - The potential for oral transmission of syphilis (A3),
  - The benefits of identifying infection early (A3), and
  - The need for prompt evaluation and therapy for sex partners (A3).

Syphilis and other STIs are transmitted primarily through close physical contact involving genital, rectal, or oral mucosal surfaces. Patients should be informed about the risk of acquiring syphilis at all sites of possible exposure and about oral transmission, which is a route that is often not considered [CDC 2002]. Education about the value of condom use should also be provided. Consistent and correct condom use may reduce the risk of syphilis acquisition by up to 70% [Holmes, et al. 2004]; however, clinicians should inform patients that syphilis may be transmitted at areas that are not covered by a condom, such as the groin [Koss, et al. 2009] or mouth.

In patients with HIV, syphilis acquisition poses additional risk because genital ulcer disease has been associated with an increased risk of HIV transmission to sex partners who do not have HIV [Telzak, et al. 1993; Dickerson, et al. 1996; Fleming and Wasserheit 1999]. Importantly, the presence of herpes simplex virus, syphilis, or chancroid ulcers in patients with HIV directly increases the likelihood that genital secretions will contain an infectious amount of HIV-1 that may come in contact with genital mucosal cells receptive to HIV-1 infection.

Screening

RECOMMENDATIONS

Serologic Screening

- Clinicians should obtain serologic screening for syphilis at least annually for all patients with HIV (see Table 2: Screening and Diagnostic Tests for Syphilis and Table 3: Interpretation of Results of Reverse-Sequence Testing for Syphilis). (A2)

- In response to the current epidemiology in NYS, clinicians should perform syphilis screening every 3 months (A3) for HIV-infected men who have sex with men (MSM) at highest risk of syphilis infection, including those who:
  - Report, or whose partners report, multiple or anonymous sex partners. (A3)
  - Have been, or whose sex partners have been, diagnosed with or treated for a bacterial sexually transmitted infection (STI) since the last evaluation. (A3)
  - Engage, or whose sex partners may engage, in sexual activity at sex parties or other high-risk venues. (A3)
  - Are involved, or whose sex partners may be involved, in transactional sex (e.g., sex workers and their clients). (A3)
  - Report recreational substance use during sexual activity. (A3)
  - Self-identify as at high risk of STIs. (A3)
RECOMMENDATIONS

Screening in Pregnancy

- Clinicians should obtain serologic screening for syphilis for pregnant patients with HIV at the first prenatal visit, during the third trimester (28-32 weeks of gestation), and at delivery. (A2)


Frequency

All patients with HIV should be screened for syphilis at least once per year. Diagnosis of syphilis during the primary and secondary stages of disease, which occur within the first year after infection, not only requires less-intensive treatment than at later stages but also allows for earlier identification and treatment of sex partners.

Men who have sex with men (MSM) who engage, or whose partners may engage, in continued high-risk behavior should be screened for syphilis at least every 3 months. Factors that may prompt more frequent screening include multiple or anonymous sex partners, sexual activity at sex parties or other high-risk venues, or involvement in transactional sex (e.g., sex workers and their clients) [Golub, et al. 2016]. The diagnosis of another bacterial STI in a patient with HIV or a patient’s sex partner should prompt a clinician to perform a syphilis screening test and to consider more frequent screening for syphilis. Intensified syphilis screening for MSM at high risk may increase the identification of early or secondary syphilis, and early intervention may decrease the duration of infectiousness [Bissessor, et al. 2010]. Nearly every region in New York State (NYS) reported an increase in the incidence of syphilis infections in 2015, with the overwhelming majority of cases occurring among MSM [NYSDOH 2014].

Congenital syphilis cases increased by 185% in the United States between 2014 and 2018 [CDC 2019] and by 200% in NYS outside of New York City (NYC) during that same time frame [NYSDOH unpublished data]. NYC experienced a 185% increase in congenital syphilis cases from 2017 to 2018 [NYSCDHMH 2019]. An investigation of 68 cases of congenital syphilis from NYC published in 2018 revealed that screening for syphilis did not occur prior to delivery in 37% of cases due to a lack of prenatal care (21/26) or lack of a performed screening test during care (5/26). Another 30% of identified cases occurred in individuals who acquired syphilis during pregnancy but after receiving a time-appropriate non-reactive screening test result [Slutsker, et al. 2018]. Given the historically high rates of congenital syphilis in NYS, recent data regarding acquisition of syphilis during pregnancy and the known benefits of treatment of syphilis during pregnancy, this committee recommends an additional screening test be performed early in the third trimester at 28 to 32 weeks of gestation. Other entities, including the U.S. Preventive Services Task Force (USPSTF) [Curry, et al. 2018], the 2015 CDC STD Treatment Guidelines [Workowski and Bolan 2015], the American College of Obstetrics and Gynecology (ACOG) and the American College of Pediatrics [AAP and ACOG 2017], recommend screening at the first visit and at delivery during all pregnancies and recommend third-trimester screening for all pregnant individuals at high risk of exposure and after exposure to an untreated sex partner. Individuals who live in high-prevalence communities, or have HIV, or have a history of incarceration or commercial sex work are considered at high risk of exposure [Curry, et al. 2018]. In April, 2018, the NYC Department of Health and Mental Hygiene also recommended screening for syphilis at first visit, at 28 weeks of gestation, and at delivery for all pregnant patients [NYSCDHMH 2019].

→ KEY POINTS

- STI screening should be performed every 3 months for persons at high risk regardless of the frequency of their HIV monitoring visits.
- Regular assessment of ongoing risk behavior enables clinicians to determine the appropriate frequency of screening. Clinicians can seek training to enhance their comfort with sexual history-taking and to develop nonjudgmental approaches to educating patients about the importance of STI screening.
- The NYSDOH Clinical Education Initiative and the New York City STD/HIV Prevention Training Center provide HIV-related educational resources and training for providers.

Laboratory tests used in screening for syphilis are described in Table 2: Screening and Diagnostic Tests for Syphilis, below, with additional information in Table 3: Interpretation of Results of Reverse-Sequence Testing for Syphilis, in the guideline.
section on *Syphilis and Neurosyphilis: Presentation, Diagnosis, and Reporting*, illustrate the standard and reverse protocols for syphilis screening and diagnosis.

**Serologic Testing**

**Nontreponemal tests**: Rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) are nonspecific quantitative tests that result from the cross-reaction of human cardiolipin-lecithin in syphilis infection. The tests correlate with disease activity and are used to follow the clinical course and determine the effectiveness of treatment. During primary syphilis, the nontreponemal tests usually become positive approximately 7 to 10 days after the onset of the chancre.

→ **KEY POINT**

- Because the nontreponemal tests are negative in approximately 20% of cases presenting with a chancre (i.e., primary ulcer), patients presenting with an ulcer that has the clinical presentation of a chancre (painless, indurated ulcer with a clean base and smooth borders) should be tested with both treponemal and nontreponemal tests and should receive presumptive treatment for primary syphilis (see the Treatment and Follow-Up section of this guideline).

The sensitivity of these tests is near 100% during secondary syphilis. Serum reagin levels are typically low (<1:8) in primary syphilis and higher (>1:32) in secondary syphilis; serum reagin levels are variable thereafter and may serorevert to negative in approximately 25% of untreated patients (usually 2 years after the infection). Serum samples containing large amounts of nontreponemal reagin occasionally demonstrate a false-negative reaction, known as a prozone reaction [Jurado, et al. 1993]. When there is clinical suspicion for syphilis but the nontreponemal test result is negative, clinicians should order laboratory dilution and retesting of the sample. Many laboratories perform dilution as part of their internal protocol; however, in highly suspicious cases with negative nontreponemal tests, communication with the laboratory is necessary to confirm that the sample was retested after dilution. Nontreponemal tests may be false-positive in the setting of medical conditions other than syphilis, including HIV infection; collagen vascular diseases; narcotic drug use; advanced age; pregnancy; chronic liver disease; some viral infections, such as Epstein-Barr virus; and other chronic inflammatory conditions (i.e., biological false-positive nontreponemal test) [Hernandez-Aguado, et al. 1998; CDC 2011; Park, et al. 2011].

**Treponemal tests**: The fluorescent treponemal antibody test, *T. pallidum* particle agglutination, and syphilis IgG or IgG/IgM enzyme-linked immunosorbent assay or enzyme immunoassay/chemiluminescence immunoassay tests are treponemal assays that measure antibody to surface protein of *T. pallidum*. The treponemal tests are more specific than nontreponemal tests and become reactive approximately 7 to 10 days after the appearance of the chancre. A treponemal test should be explicitly ordered during primary infection. Treponemal tests do not correlate with disease activity and remain positive for life in approximately 80% of patients, even after effective treatment.

| Table 1: Sensitivity of Serological Tests in Untreated Syphilis*† |
|---------------------------------|------------------|-----------------|-----------------|-------|
| **Test**                        | **Stage of Disease (Percent Positive [Range])** |                  |                  |      |
|                                 | **Primary**      | **Secondary**   | **Latent**      | **Tertiary** |
| VDRL                            | 78 (74-87)       | 100             | 95 (88-100)     | 71 (37-94) |
| RPR                             | 86 (77-99)       | 100             | 98 (95-100)     | 73     |
| FTA-Abs*                        | 84 (70-100)      | 100             | 97 (97-100)     | 96     |
| Treponemal Agglutination*       | 76 (69-90)       | 100             | 97 (97-100)     | 94     |
| EIA, enzyme immunoassay         | 93               | 100             | 100             | —      |

*EIA, enzyme immunoassay; FTA-Abs, fluorescent treponemal antibody test; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory.

*FTA-Abs and *T. pallidum* particle agglutination are generally considered equally sensitive in the primary stage of disease.

†Reprinted from Centers for Disease Control and Prevention [CDC 2013].
Considerations for serology in patients with HIV: Serologic test results for the majority of patients with HIV and syphilis are consistent with those seen in non-HIV-infected patients with syphilis; however, there have been reports of atypical serologies in patients coinfected with HIV and syphilis as described below:

- Patients with HIV may have false-positive nontreponemal reagin test results (RPR/VDRL). In one study, 4% of patients with HIV tested had false-positive RPR results [Rompalo, et al. 1992].
- Seroreactivity may be delayed or absent in patients with HIV. Rare cases have been reported of biopsy-proven secondary syphilis in patients with HIV with negative syphilis serologies [Tikjob, et al. 1991].
- Patients with HIV may have higher mean serologic serum nontreponemal reagin levels than do patients without HIV [Rolfs, et al. 1997].
- No correlation has been found between serologic response to therapy and CD4 count [Rolfs, et al. 1997].
- Prozone reaction occurs more commonly in patients with HIV [Schofer, et al. 1996].

Lesion-Based Testing (Identification of *T. Pallidum*)

Direct fluorescent antibody test: A direct fluorescent antibody test can be performed on lesion exudate or tissue specimen. There are no differences in test performance characteristics among patients with and without HIV.

Darkfield microscopy: Examination of exudate from an ulcer base or a mucocutaneous lesion under darkfield microscopy can identify the spirochete (*T. pallidum*). This test is invalid for oral samples and is typically available only in specialized centers; local health department may be consulted for availability. There are no differences in test performance characteristics among patients with and without HIV.

Silver stain: Spirochetes may be seen in biopsy specimens of suspicious lesions such as palmar macular rash or gummatous lesions. There are no differences in test performance characteristics among patients with and without HIV.

Polymerase chain reaction (PCR): PCR can be performed on specimens of lesions to detect DNA from *T. pallidum*. In comparison with swab, the sensitivity of PCR is significantly lower when samples from peripheral blood mononuclear cell, plasma, serum, and whole-blood fractions are used [Grange, et al. 2012].

Obtaining a Sexual History

<table>
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<th>RECOMMENDATIONS</th>
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<tbody>
<tr>
<td><strong>Sexual History</strong></td>
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<tr>
<td>• Clinicians should ask all patients about sexual behaviors and new sex partners at each routine monitoring visit to assess for risk behaviors that require repeat or ongoing screening. (A3)</td>
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When obtaining a sexual history, questions should focus primarily on the patient’s sexual behavior and not solely on sexual and gender identity (e.g., avoid use of such labels as “lesbian,” “homosexual,” or “gay” or “transgender”). A study conducted in New York City found that self-reported sexual identity could not independently establish patients’ risk. Many men who have sex with men (MSM) in the study did not identify as “gay,” underscoring the importance of assessing sexual behavior when determining a patient’s risk [Pathela, et al. 2006; Bernstein, et al. 2008]. Transgender people differ widely in terms of sexual behavior and anatomy. It is helpful to ask about the type of sex a person is having and the parts of anatomy used for sex, as well as about the anatomy of partners [CETH 2016]. A patient’s openness to discuss his or her sexual and gender identity may be important for the clinician’s understanding of health status and the individual’s perceived stigma and ability to accurately assess the patient’s risk of acquiring or transmitting STIs. Therefore, clinicians should stress the confidential nature of discussions about sexual activities and maintain a nonjudgmental attitude to encourage patients to disclose all sexual behaviors.

For clinicians who are uncomfortable discussing sexual behaviors and sexually transmitted infection (STI) transmission risk, training may help increase their comfort level and assist them in developing a nonjudgmental approach to educating patients about the importance of STI screening. The New York State (NYS) Department of Health (NYSDOH) Clinical Education Initiative Line (866-637-2342) enables clinicians in NYS to discuss post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP), HIV, hepatitis C virus (HCV), and STI management with a specialist, and the New York City
STD/HIV Prevention Training Center provides HIV-related educational resources and training for providers. The Centers for Disease Control and Prevention’s *Guide to Taking a Sexual History* offers parameters for discussing sexual health issues with patients.

**Syphilis and Neurosyphilis: Presentation, Diagnosis, and Reporting**

**RECOMMENDATIONS**

### Presentation and Diagnosis

- As part of the initial and then annual comprehensive physical examination for patients with HIV, clinicians should examine all skin and mucosal surfaces for lesions, especially less-visible areas, such as the anus, cervix, vagina, vulva, urethra, oropharynx, and under the foreskin in uncircumcised males. (A3)
- Clinicians should perform a neurologic review of systems, including ophthalmologic and otic, for all patients with HIV who are diagnosed with syphilis and follow up with further neurologic evaluation, as recommended in *Table 4. Recommended Treatment and Follow-Up of Syphilis in Patients with HIV.* (A2)
- Clinicians should ensure that two-stage syphilis testing is performed by the laboratory if the initial screen is reactive. (A1)
- Clinicians should perform a nontreponemal test, such as the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) test, for repeat screening in patients who have a history of syphilis infection. (A1)
- Clinicians should include neurosyphilis in the differential diagnosis of all patients with HIV who present with neurologic, ophthalmologic, otic, or neuropsychiatric signs or symptoms. (A2)
- Clinicians should perform a lumbar puncture in patients with HIV who have syphilis or a history of syphilis when patients present with the following:
  - Neurologic, ophthalmologic, otic, or neuropsychiatric signs or symptoms that are not explained by another etiology. (A2)
  - Evidence of treatment failure (see *Treatment Failure* in the *Treatment and Follow-Up* section of this guideline). (A2)
  - Evidence of active tertiary syphilis (aortitis, gummas). (A3)

### Reporting: New York State Requirement

- Clinicians must report all suspected or confirmed syphilis diagnoses to the local health department of the area where the patient resides according to NYS requirements.
  - See *NYSDOH Communicable Disease Reporting* and *NYC Health Reporting Diseases and Conditions*.

### Presentation

Syphilis is classified into four stages: primary, secondary, latent, and tertiary. Syphilis transmission occurs during the primary or secondary clinical stage of infection. Latent syphilis, by definition, has no associated symptoms or signs. Because the chances of primary syphilis are usually painless and may go unnoticed by the patient, it is important that the clinician examine all skin and mucosal surfaces of patients with HIV during the annual comprehensive physical examination. However, most cases of syphilis are diagnosed in the latent phase [Ratnam 2005] and thus lack all signs or symptoms at the time of presentation.

Most patients with syphilis and HIV coinfection present with the signs and symptoms typical of syphilis in patients without HIV [Larsen, et al. 1995]. However, published case reports have described atypical syphilis in the setting of HIV coinfection [Workowski and Bolan 2015]. *Differences in Clinical Presentation of Syphilis in Patients With and Without HIV* summarizes the usual clinical presentation of symptomatic syphilis and the atypical clinical presentation of syphilis in individuals with
HIV coinfection (see also: Photographic Examples of Secondary Syphilis in Patients With HIV). The lesions of primary syphilis usually develop after an incubation period of 10 to 90 days (usually 3 weeks). Primary lesions usually last 3 weeks and resolve without treatment. The onset of secondary syphilis occurs from 2 weeks to 6 months (usually 4 weeks) after the resolution of the primary stage. Secondary symptoms usually last 4 weeks and, like primary symptoms, resolve without treatment. Latent syphilis may persist for up to 50 years after infection. Latent infection is divided into early latent (<1 year since infection) and late latent (≥1 year after infection). During early latent infection, relapse of secondary syphilis with subsequent transmission to sexual partners is possible [Golden, et al. 2003]. Tertiary syphilis refers to clinical manifestations occurring after the latent stage (range, 2-50 years after latency). Typically, tertiary syphilis is divided by organ system involvement into gummatous, cardiovascular, and neurologic syphilis. Patients with syphilis who have signs or symptoms of the disease are classified into the appropriate stage based on the physical examination.

Syphilis is known to have a wide variety of clinical manifestations, including the following:

- It may mimic other infections, such as herpes, fungal rash, or noninfectious dermatologic conditions, such as contact dermatitis or psoriasis.
- Syphilitic gumma may present as a focal mass lesion.
- Ocular syphilis may develop at any part of the eye during any stage of syphilis infection (including primary or secondary syphilis) and may cause permanent blindness without prompt treatment; manifestations are bilateral in up to 50% of cases [Spoor, et al. 1983; Kiss, et al. 2005; Mathew, et al. 2014; Dombrowski, et al. 2015].
- Otophylis may develop at any stage of syphilis infection, causing tinnitus, vertigo, and permanent hearing loss even after treatment [Hendershot 1973; Wong, et al. 1977; Dobbin and Perkins 1983; Steckelberg and McDonald 1984; Gleich, et al. 1992].
- Frequency of clinical relapse or progression after syphilis treatment may be higher in the setting of HIV.

Syphilis should be included as part of the differential diagnosis for patients presenting with oral, genital, cervical, or anal lesions; rash; eye disease or vision complaints; aortitis; or neurologic disease (see the Presentation and Diagnosis of Neurosyphilis section, below, for information about signs, symptoms, and diagnosis of neurosyphilis).

**Diagnosis**

Syphilis is diagnosed primarily through the use of laboratory testing. Findings from the patient’s medical history and physical examination are used to determine stage of disease. The overwhelming majority of cases are identified through the use of syphilis serology (antibody) tests. Lesion-based testing may identify the causative organism when a lesion is present (see Table 2: Screening and Diagnostic Tests for Syphilis, below). Definitive diagnosis of syphilis is made either serologically or, if available, by direct identification of the causative organism.

Syphilis serologies are complex and require two-stage testing as described in Figures 2 and 3, below. Note the following features of syphilis serologies relevant to diagnosis:

- Antibody requires time to develop, and all serologic tests may be negative very early in infection, even shortly after a chancre has appeared. Lesion-based testing with darkfield microscopy or presumptive diagnosis on the basis of lesion appearance may be the only means of diagnosis in these situations. (For more information, see Table 2: Screening and Diagnostic Tests for Syphilis, below.)
- RPR tests performed during the secondary stage may appear falsely nonreactive when antibody levels are exceedingly high, a phenomenon known as the prozone effect. In this circumstance, the specimen should be diluted and retested if suspicion for syphilis is high.

Although there are limited data available specifically regarding the rate of syphilis coinfection identified in patients with gonococcal or chlamydial infections, surveillance reports identify high rates of gonococcal or chlamydial infections and syphilis among men who have sex with men. Because exposure resulting in the acquisition of one sexually transmitted infection (STI) has long been recognized to be a risk for other STIs and HIV infection, this Committee recommends testing for gonorrhea and chlamydia when a patient is diagnosed with a new syphilis infection [Bala, et al. 2011; Foschi, et al. 2014; CDC 2017a].
Table 2: Screening and Diagnostic Tests for Syphilis

<table>
<thead>
<tr>
<th>Serologic Tests</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Nontreponemal:</strong></td>
<td>Nonspecific quantitative tests</td>
</tr>
<tr>
<td>• Rapid plasma reagin (RPR)</td>
<td>May be negative in 15% to 25% of cases presenting with primary chancre [Larsen, et al. 1995; CDC 2013]</td>
</tr>
<tr>
<td>• Venereal disease research laboratory (VDRL)</td>
<td>Near 100% sensitivity during secondary syphilis [Larsen, et al. 1995; CDC 2013]</td>
</tr>
<tr>
<td></td>
<td>May be positive in the setting of medical conditions other than syphilis, including HIV infection; collagen vascular diseases; narcotic drug use; advanced age; pregnancy; chronic liver disease; some viral infections, such as Epstein-Barr virus; and other chronic inflammatory conditions</td>
</tr>
<tr>
<td><strong>Treponemal:</strong></td>
<td>Measure antibody to surface protein of pallidum (antibodies will persist; they do not afford protective immunity and cannot be used to diagnose subsequent episodes or to monitor response to therapy)</td>
</tr>
<tr>
<td>• Fluorescent treponemal antibody absorbed (FTA-Abs)</td>
<td>More specific than nontreponemal tests</td>
</tr>
<tr>
<td>• <em>pallidum</em> particle agglutination (TP-PA)</td>
<td>Become reactive approximately 7 to 10 days after the appearance of the chancre</td>
</tr>
<tr>
<td>• <em>pallidum</em> IgG + IgM enzyme-linked immunosorbent assay (ELISA)</td>
<td>Rarely produce false-positive results [Hernandez-Aguado, et al. 1998; CDC 2011; Park, et al. 2011]</td>
</tr>
<tr>
<td>• Treponemal enzyme immunoassay (EIA)/chemiluminescence immunoassay (CIA)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion-Based Tests [c]</th>
<th>Description [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Direct fluorescent antibody test (DFA)</td>
<td>Performed on lesion exudate or tissue specimen</td>
</tr>
<tr>
<td>• Darkfield microscopy</td>
<td>Performed on exudate from an ulcer base or a mucocutaneous lesion</td>
</tr>
<tr>
<td>• Silver stain</td>
<td>Performed on biopsy specimens of suspicious lesions, such as palmar macular rash or gummatous lesions</td>
</tr>
<tr>
<td>• Polymerase chain reaction (PCR)</td>
<td>Performed on specimens of lesions</td>
</tr>
</tbody>
</table>

Notes:
- Some clinical laboratories and blood banks use the *pallidum* IgG + IgM ELISA or treponemal CIA/EIA assay first, followed by nontreponemal tests.
- Lesion-based testing is used when serologic testing is nonreactive in the presence of a lesion.

Traditionally, the standard screening algorithm for syphilis has started with a nontreponemal screening test (e.g., RPR or VDRL), followed by a confirmatory test for treponemal antigen (e.g., *T. pallidum* particle agglutination [TP-PA], fluorescent treponemal antibody absorbed [FTA-Abs], or enzyme immunoassay [EIA]/chemiluminescence immunoassay [CIA]). Figure 2, below, details the standard screening algorithm for syphilis.
Figure 2: Standard Protocol for Syphilis Screening and Diagnosis [AIDSinfo 2017]

Figure 3: Alternative, Reverse Algorithm for Syphilis Screening and Diagnosis [CDC 2011; AIDSinfo 2017]
Some laboratories use a reverse-sequence screening algorithm with automated treponemal EIA or CIA as the initial screening test, followed by confirmation with the nontreponemal RPR (Figure 3: Alternative, Reverse Algorithm for Syphilis Screening and Diagnosis). When discordant results are provided by laboratories using the alternative algorithm (i.e., reactive EIA/CIA with a nonreactive RPR), the Centers for Disease Control and Prevention recommend that a second different treponemal test (ideally based on different antigens than the first test) be performed to confirm the results of the first nonspecific antibody result. Clinicians should request information regarding the screening algorithm of their laboratory and be familiar with the testing sequence used. Table 3: Interpretation of Results of Reverse-Sequence Testing for Syphilis, below, provides recommendations for interpreting results when the reverse algorithm is used.

### Difficulties with interpreting syphilis serologies
Serologic test results are negative in patients with incubating syphilis, and the sensitivity of serologic tests is approximately 80% during the early primary stage of syphilis (i.e., within the first 10 days after the lesion appears). All syphilis serologic tests may be falsely negative early in infection, including at the initial appearance of the syphilitic chancre. Serum samples containing large amounts of nontreponemal reagin rarely, but occasionally, demonstrate a false-negative reaction, known as a prozone reaction [Jurado, et al. 1993]. When there is clinical suspicion of syphilis but the nontreponemal test result is negative, clinicians should order laboratory dilution and retesting of the sample. Treponemal tests rarely produce false-negative results; however, if clinical suspicion is high, an alternative treponemal test should be considered. See Table 1: Sensitivity of Serological Tests in Untreated Syphilis for the sensitivity of tests during various stages of untreated syphilis.

### Table 3: Interpretation of Results of Reverse-Sequence Testing for Syphilis [CDC 2011; AIDSinfo 2017]

<table>
<thead>
<tr>
<th>T. pallidum EIA/CIA Test</th>
<th>RPR Test</th>
<th>Second Treponemal-Specific Test (e.g., TP-PA)</th>
<th>Interpretation and Action</th>
</tr>
</thead>
</table>
| Positive                 | Positive | Not necessary                                | • Current or past syphilis (treated or untreated)  
|                          |          |                                             | • Assess for treatment    |
| Positive                 | Negative | Positive                                    | • Current or past syphilis (treated or untreated)  
|                          |          |                                             | • Assess for treatment    |
| Negative                 | Not performed in the algorithm | Not performed in the algorithm | • No syphilis  
|                          |          |                                             | • Consider alternative treponemal test if clinical suspicion is high  
| Positive                 | Negative | Negative                                    | • No syphilis  
|                          |          |                                             | • Consider alternative treponemal test if clinical suspicion is high  

CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; RPR, rapid plasma reagin; TP-PA, T. pallidum particle agglutination.

The persistence of syphilis antibody complicates the diagnosis of a new infection in those with a history of prior syphilis. With the exception of 15% to 25% of individuals who receive treatment during primary infection [Romanowski, et al. 1991], most individuals with a history of syphilis infection will experience lifelong positivity for FTA-Abs, TP-PA, enzyme-linked immunosorbent assay, and EIA. Some individuals previously treated for syphilis will continue to have a low-positive serum RPR or VDRL (i.e., “serofast” syphilis). A 4-fold or greater increase in serum RPR or VDRL may indicate treatment failure or a reinfection with syphilis. Use of the same nontreponemal reagin test and, ideally, the same laboratory when performing repeat screening and monitoring response to treatment will allow for accurate comparison of titers and reduce variations in reagin levels across assays.

### Presentation and Diagnosis of Neurosyphilis
Central nervous system involvement can occur at any stage of syphilis. Neurologic signs and symptoms, which may include, but are not limited to, meningoitis or ophthalmologic or otologic abnormalities, warrant examination of the CSF, regardless of the stage of syphilis. Patients may also present with neuropsychiatric signs or symptoms, such as a change in cognition or behavior [Mitsonis, et al. 2008]. Any evidence of tertiary syphilis or treatment failure is also an indication for CSF examination. Diagnosis of neurosyphilis requires examination of the cerebrospinal fluid (CSF); the diagnosis is definitive when a CSF VDRL is reactive, unless the CSF is contaminated with blood. When a CSF VDRL test is nonreactive, other CSF abnormalities may be consistent with a diagnosis of neurosyphilis. Both CSF pleocytosis and elevated CSF protein have been associated with neurosyphilis. However, these nonspecific CSF abnormalities may also be found in...
patients with HIV because of the HIV infection itself or other HIV-associated conditions, making the results of CSF VDRL-negative examinations difficult to interpret.

Detection of the causative organism in the CSF in early syphilis is not more common in patients with HIV, does not correlate with subsequent development of neurosyphilis, and is not linked to serologically defined treatment failure. For these reasons, most experts do not recommend routine CSF examination for patients with HIV whose early syphilis does not present with neurologic symptoms. However, some clinicians would favor treating more aggressively (with a regimen recommended for late latent syphilis) upon diagnosis to prevent future complications.

One prospective study that analyzed the CSF test results of 326 patients with syphilis found that patients with HIV and syphilis who had RPR serum reagin levels ≥1:32 or who had CD4 counts ≤350 cells/mm³ were more likely to have neurosyphilis [Marra, et al. 2004]. However, CSF examination in the absence of neurological signs or symptoms has not been shown to improve clinical outcome [Workowski and Bolan 2015].

**Reporting: New York State**

**Requirements:** Prompt reporting of suspected or confirmed syphilis is mandated under the NYS Sanitary Code (10NYCRR 2.10). In NYS, syphilis cases should be reported immediately to the local health department as follows:

- By telephone:
  - Any positive primary or secondary stage disease.
  - Any positive prenatal or delivery test, regardless of serum reagin level.
  - Any nontreponemal test ≥1:16.

**For more information about disease reporting in NYS:** Contact the local health department where the patient resides or the NYSDOH Bureau of Communicable Disease Control at 518-473-4439.

**Partner notification:** The local health department may contact the patient for epidemiological investigation or to offer assistance with partner notification.

Clinicians can contact local health departments to obtain previously reported nontreponemal and treponemal test results and treatment histories. See *STD Clinics in NYS* for contact information for clinics in each county.

**Reporting: New York City**

**Requirements:** NYC’s Health Code Article 11 requires prompt reporting of all cases of syphilis (see *NYC DOHMH Diseases and Conditions Reporting*). In NYC, syphilis cases can be reported using the *Universal Reporting Form*, which can be submitted as follows:

- Online: via NYCMED
- Fax: call 866-692-3641 for the appropriate fax number
- Mail: New York City Department of Health and Mental Hygiene (NYC DOHMH), 42-09 28th Street, CN-22, Long Island City, NY 11101.

**For more information:** See *How to Report Diseases, Events, and Conditions to the New York City Health Department* for more information.

**Partner notification:** The NYC DOHMH may contact the patient for epidemiological investigation or to offer assistance with partner notification.
## Differences in Clinical Presentation of Syphilis in Patients With and Without HIV

<table>
<thead>
<tr>
<th>Stage of Syphilis</th>
<th>Reported in All Patients</th>
<th>Reported in Patients with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Develops 10-90 days (usually 3 weeks) after exposure</td>
<td>- Multiple chancres</td>
</tr>
<tr>
<td></td>
<td>- Single chancre: painless, indurated ulcer with a clean base and smooth borders</td>
<td>- Chancres that are larger, deeper, and resolve more slowly</td>
</tr>
<tr>
<td></td>
<td>- Chancre persists 1-5 weeks (average 3 weeks) and heals spontaneously, regardless of treatment</td>
<td>- Atypical chancres appearing as abrasions or fissures</td>
</tr>
<tr>
<td></td>
<td>- Painless, rubbery lymphadenopathy in some cases</td>
<td>- Reports of ocular syphilis, mainly uveitis (found in 10% of patients with a positive CSF VDRL in one study); patients should receive treatment for neurosyphilis</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Signs and symptoms occur 2 weeks to 6 months (usually 4 weeks) after resolution of primary syphilis</td>
<td>- Coincident chancres with signs of secondary syphilis</td>
</tr>
<tr>
<td></td>
<td>- Low-grade fever, adenopathy, headache, malaise, and rash may occur</td>
<td>- Duration of rash may be slightly longer, and rash may be more widespread</td>
</tr>
<tr>
<td></td>
<td>- Maculopapular rash involving palms and soles, mucous patches in the mouth, condylomata, and patchy alopecia (persists 2-6 weeks and heals spontaneously) are common</td>
<td>- Atypical skin rashes, including papular, nodular, and ulceronodular (lues maligna)</td>
</tr>
<tr>
<td></td>
<td>- Uveitis, iritis, hepatitis, and nephrotic syndrome may occur</td>
<td>- Reports of ocular syphilis, mainly uveitis (found in 10% of patients with a positive CSF VDRL in one study); patients should receive treatment for neurosyphilis</td>
</tr>
<tr>
<td><strong>Latent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Infection can be detected by serologic testing but otherwise lacks evidence of disease</td>
<td>- Retinitis, papillitis, and cranial nerve abnormalities II, III, or V in association with syphilitic meningitis; patients should receive treatment for neurosyphilis</td>
</tr>
<tr>
<td></td>
<td>- Can persist up to 50 years past initial infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Early latent syphilis: latent syphilis acquired within the preceding year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Diagnosis of early latent syphilis can be made if any of the following occur in the year preceding the evaluation:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Seroconversion was documented (i.e., documented nonreactive nontreponemal test within preceding 12 months)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 4-fold increase in nontreponemal serum reagin since the last adequately treated infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- A history of unequivocal symptoms of primary or secondary syphilis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Sex partner documented to have primary, secondary, or early latent syphilis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Reports of ocular syphilis, mainly uveitis (found in 10% of patients with a positive CSF VDRL in one study); patients should receive treatment for neurosyphilis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- All other asymptomatic cases are either late latent syphilis or latent syphilis of unknown duration</td>
<td></td>
</tr>
<tr>
<td><strong>Tertiary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gummatous (late benign syphilis)</strong></td>
<td>- Occurs 1 to &gt;40 years (average 4-10 years) after initial infection</td>
<td>- Several reports of gummas</td>
</tr>
<tr>
<td></td>
<td>- Gumma-indolent lesion that consists of a marked granulomatous response on histopathology</td>
<td>- One case of rapid progression to gumma within several months of a chancre</td>
</tr>
<tr>
<td></td>
<td>- Occurs in any organ system</td>
<td>- Located in multiple organ systems including the brain</td>
</tr>
<tr>
<td></td>
<td>- Rare in the antibiotic era</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>- Occurs after 15-30 years of latency</td>
<td>- Rare cases of rapidly developing aortitis</td>
</tr>
<tr>
<td></td>
<td>- Pathologic lesion is endarteritis obliterans of vasa vasorum of the aorta</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- May result in aneurysms, coronary artery stenosis, or aortic regurgitation</td>
<td></td>
</tr>
</tbody>
</table>
Table B1: Differences in Clinical Presentation of Syphilis in Patients With and Without HIV [see references below]

<table>
<thead>
<tr>
<th>Stage of Syphilis</th>
<th>Reported in All Patients</th>
<th>Reported in Patients with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>- Rare in the antibiotic era</td>
<td>- Numerous case reports of neurosyphilis</td>
</tr>
<tr>
<td></td>
<td>- Asymptomatic or symptomatic meningitis (early after infection)</td>
<td>- Progression to neurosyphilis despite treatment of early syphilis</td>
</tr>
<tr>
<td></td>
<td>- Meningovascular syphilis presenting as cerebrovascular accident</td>
<td>- Reports of rapid progression to neurosyphilis without long latency</td>
</tr>
<tr>
<td></td>
<td>- Parenchymatous syphilis presenting as general paresis (&gt;20 years after initial infection) or tabes dorsalis (15-20 years after initial infection)</td>
<td>- Cases have occurred in patients with both normal and low CD4 counts</td>
</tr>
<tr>
<td></td>
<td>CSF, cerebrospinal fluid; VDRL, venereal disease research laboratory.</td>
<td>- Clinical features include asymptomatic disease, meningitis, cranial nerve deficits, optic neuritis, myelitis, stroke, and cerebral gummas</td>
</tr>
<tr>
<td></td>
<td>- Reports of ocular syphilis, mainly uveitis during secondary syphilis (found in 10% of patients with a positive CSF VDRL in one study); patients should receive treatment for neurosyphilis</td>
<td>- Reports of ocular syphilis, mainly uveitis during secondary syphilis (found in 10% of patients with a positive CSF VDRL in one study); patients should receive treatment for neurosyphilis</td>
</tr>
<tr>
<td></td>
<td>- Retinitis, papillitis, and cranial nerve abnormalities II, III, or V in association with syphilitic meningitis during secondary syphilis; patients should receive treatment for neurosyphilis</td>
<td>- Retinitis, papillitis, and cranial nerve abnormalities II, III, or V in association with syphilitic meningitis during secondary syphilis; patients should receive treatment for neurosyphilis</td>
</tr>
</tbody>
</table>

Table References


**Photographic Examples of Secondary Syphilis in Patients With HIV**

(From the slide collection of The Ronald O. Perelman Department of Dermatology, New York University School of Medicine.)

**Malignant syphilis (lues maligna) or ulceronodular secondary syphilis:** Patient with HIV
**Nodular secondary syphilis:** Patient with HIV

![Image of nodular secondary syphilis](image1.png)

**Granulomatous papules and nodules:** Face of a patient with HIV

![Image of granulomatous papules and nodules](image2.png)

**Diffuse roseola-like eruption (roseola syphilitica):** Trunk, limbs, and acral surfaces in a patient with HIV

![Image of diffuse roseola-like eruption](image3.png)

**Dull-red to copper-colored macules, papules, or plaques:** Seen on the palms in secondary syphilis

![Image of dull-red to copper-colored macules](image4.png)

**Almar plaques with a collarette of scale (collarette of Biett)**

![Image of Almar plaques with a collarette of scale](image5.png)
Dull-red to copper-colored macules, papules, or plaques: Seen on the soles in secondary syphilis

Multiple discrete flat papules of lenticular syphilis

Annular and figurate plaques

Mucous patches are superficial mucosal erosions: Seen in secondary syphilis. They can be found on any mucosal surface and are highly infectious.
Condyloma lata: More common in the anogenital area. This example is on the tongue. The thin macerated plaques can resemble flat or genital warts. These are also highly infectious.

Treatment and Follow-Up

RECOMMENDATIONS

Treatment

- Because of the possibility of false-negative test results in primary syphilis, clinicians should presumptively treat patients at risk of syphilis who present with a lesion typical of a syphilitic chancre. (A3)
- Clinicians should use long-acting benzathine penicillin G as the recommended treatment for syphilis in patients with HIV. (A2)
  - See Table 4. Recommended Treatment and Follow-Up of Syphilis in Patients with HIV for dose and frequency according to stage of syphilis.
- Clinicians should use only penicillin to treat all stages of syphilis in pregnant patients. (A2)
- Clinicians should obtain baseline and monthly assessment of serum nontreponemal reagin levels when treating syphilis in pregnant patients with HIV if the risk of syphilis reinfection is high. (A3)

Treatment in Penicillin-Allergic Patients

- Clinicians should administer desensitization therapy followed by penicillin therapy to treat penicillin-allergic patients who have neurosyphilis, other forms of tertiary syphilis, syphilis in pregnancy, or syphilis that cannot be treated by an alternative regimen. (A2)
- Clinicians should administer desensitization therapy for patients with HIV, followed by penicillin therapy, rather than attempt alternate therapies if adherence to therapy or close follow-up cannot be ensured. (A3)
- Clinicians should not prescribe azithromycin to treat syphilis in patients with HIV. (A2)

Jarisch-Herxheimer Reaction

- In women treated for syphilis infection during the second half of their pregnancy, clinicians should
  - Obtain a fetal sonogram to evaluate for congenital syphilis. (A2)
  - Advise women who experience fever, contractions, or a decrease in fetal movements to seek immediate obstetric care. (A2)

Treatment Failure

- Clinicians should perform CSF examination for patients who experience treatment failure, and:
  - Initiate parenteral therapy using a recommended penicillin regimen for late latent syphilis if CSF test results are negative. (A2)
  - Treat using a recommended penicillin regimen for neurosyphilis if CSF test results are positive. (A2)

Detailed treatment and follow-up recommendations for syphilis in patients with HIV are presented in Table 4: Recommended Treatment and Follow-Up of Syphilis in Patients with HIV, below. Penicillin G is the drug of choice, and
recommendations for treatment vary by stage. Recommended penicillin G regimens are the same for patients with HIV as for patients who do not have HIV.

→ **KEY POINTS**

- To avoid use of the incorrect pharmaceutical preparation of penicillin, clinicians should ensure that long-acting benzathine penicillin G (i.e., Bicillin LA and not Bicillin CR) is ordered.
- Treatment failure in a person with HIV warrants cerebrospinal fluid (CSF) examination and treatment based on test results.

Patients with HIV who are diagnosed with syphilis should be monitored closely. The frequency of follow-up varies by stage (see Table 4: Recommended Treatment and Follow-Up of Syphilis in Patients with HIV, below). Follow-up should include a physical and a neurologic examination and repeat serologic testing. Treatment failure is defined as the persistence of symptoms or the development of new clinical signs or symptoms, a 4-fold (2 reagin level) increase in nontreponemal serology (e.g., rapid plasma reagin [RPR] 1:4 increases to 1:16), or a failure of nontreponemal serology to decline 4-fold (2 reagin levels) within 12 to 24 months of treatment (nontreponemal serology should decline more rapidly in patients with primary syphilis) [Workowski and Bolan 2015]. Treatment failure in a person with HIV warrants CSF examination and treatment based on results; consultation with a care provider experienced in sexually transmitted infections (STIs) is indicated. The New York State (NYS) Department of Health (NYSDOH) Clinical Education Initiative Line (866-637-2342) enables clinicians in NYS to discuss post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP), HIV, hepatitis C virus (HCV), and STI management with a specialist, and the NYC STD/HIV Prevention Training Center provides HIV-related educational resources and training for providers. For additional information about management of treatment failure, see the Treatment Failure section, below.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment [b] (A2)</th>
<th>Follow-Up Intervals (A3)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary, secondary</td>
<td>2.4 million units IM benzathine penicillin × 1 dose</td>
<td>3, 6, 9, 12, 24 months post-treatment</td>
<td>• CSF examination recommended in the presence of neurologic, ophthalmologic, or otic changes or evidence of treatment failure [c]</td>
</tr>
<tr>
<td>Early latent</td>
<td>2.4 million units IM benzathine penicillin × 1 dose</td>
<td>6, 12, 18, 24 months post-treatment</td>
<td>• CSF examination recommended in the presence of neurologic, ophthalmologic, or otic changes or evidence of treatment failure [c]</td>
</tr>
<tr>
<td>Late latent or unknown duration</td>
<td>2.4 million units IM benzathine penicillin per week × 3 weeks</td>
<td>6, 12, 18, 24 months post-treatment</td>
<td>• CSF examination recommended in the presence of neurologic, ophthalmologic, or otic changes or evidence of treatment failure [c]</td>
</tr>
<tr>
<td>Tertiary gummatous</td>
<td>2.4 million units IM benzathine penicillin per week × 3 weeks</td>
<td>6, 12, 18, 24 months post-treatment</td>
<td>• CSF examination recommended</td>
</tr>
<tr>
<td>Tertiary cardiovascular</td>
<td>2.4 million units IM benzathine penicillin per week × 3 weeks</td>
<td>6, 12, 18, 24 months post-treatment</td>
<td>• CSF examination recommended</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Aqueous crystalline penicillin G 18 to 24 million units IV daily for 10 to 14 days</td>
<td>3, 6, 9, 12, 24 months post-treatment; repeat CSF examination every 6 months until CSF cell count is normal</td>
<td>• CSF examination recommended in the presence of neurologic, ophthalmologic, or otic changes or evidence of treatment failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Some experts recommend 2.4 million units IM benzathine after parenteral penicillin to have total duration of therapy equal to that of late latent syphilis</td>
</tr>
</tbody>
</table>
Table 4: Recommended Treatment and Follow-Up of Syphilis in Patients with HIV [a]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment [b] (A2)</th>
<th>Follow-Up Intervals (A3)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CSF abnormalities (elevated total protein and/or positive CSF VDRL) may persist for prolonged periods</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; IM, intramuscular; IV, intravenous; VDRL, venereal disease research laboratory.

a. Adapted from Centers for Disease Control and Prevention [Workowski and Bolan 2015] unless otherwise noted.
b. The efficacy of non-penicillin regimens in patients with HIV is unknown. Penicillin-allergic patients should be desensitized if possible. Close clinical and serologic follow-up is necessary when non-penicillin regimens are used to treat syphilis in patients with HIV.
c. CSF examination yielding pleocytosis, increased total protein, or positive VDRL may be consistent with neurosyphilis.
d. There are no published data to inform a recommendation regarding serologic follow-up in patients treated for tertiary syphilis. Because tertiary syphilis is a late complication of syphilis, occurring after the first year of infection, this committee recommends providers utilize the serologic follow-up schedule for late, latent syphilis (6, 12, 18, 24 months post-treatment).
e. There are limited data addressing serologic follow-up of patients treated for neurosyphilis. Because neurosyphilis may occur during all stages of syphilis, this committee recommends serologic follow-up for HIV co-infected patients treated for neurosyphilis at 3, 6, 9, 12, and 24 months post-treatment.

Treatment of Syphilis in Penicillin-Allergic Patients with HIV

Penicillin is the recommended treatment for syphilis. Alternate treatment options for penicillin-allergic patients with HIV have not been well studied. Non-penicillin therapies should be used with caution. Such regimens require close clinical and serologic follow-up to identify treatment failure or relapse. See Centers for Disease Control and Prevention’s Management of Persons Who Have a History of Penicillin Allergy for information regarding penicillin desensitization.

Doxycycline (100 mg by mouth twice per day for 14 days) may be effective for treatment of early syphilis [AIDSinfo 2017]. If treatment failure occurs with doxycycline, patients should undergo desensitization to penicillin and receive penicillin treatment. Resistance and treatment failures have been documented with the use of azithromycin (2 g by mouth in a single dose) for early syphilis; this agent should be used with caution and only when treatment with penicillin or doxycycline is not feasible [AIDSinfo 2017]. Azithromycin should not be used in patients with HIV [Workowski and Bolan 2015]. Azithromycin-resistant strains may be more common within the population of men who have sex with men [CDC 2010], and the presence of azithromycin-resistant syphilis during pregnancy increases the risk of congenital syphilis [Dowell, et al. 1992; Smith, et al. 2004; Zhou, et al. 2007; Spornraft-Ragaller, et al. 2011; Marra 2015; Liang, et al. 2016; Marra 2016; Moline and Smith 2016]. Small case series have documented use of ceftriaxone for treatment of latent and neurologic syphilis, but failures have been reported. Penicillin should be used when at all possible.

Jarisch-Herxheimer Reaction

Patients should receive education about the possibility of adverse reactions to syphilis treatment, including the Jarisch-Herxheimer reaction because this is more common in patients with HIV [Roelfs, et al. 1997] and may be misinterpreted as an allergic reaction to penicillin. The Jarisch-Herxheimer reaction, which is caused by the immunologic response to the destruction of the spirochete, can occur within the first 24 hours of syphilis therapy and may require acute management. This acute febrile reaction is frequently accompanied by headache, myalgia, and/or worsening of secondary syphilis rash and occurs most often in patients with early syphilis.

→ KEY POINT

- Early labor and fetal distress are associated with the Jarisch-Herxheimer reaction. Prompt medical care should be sought by women receiving syphilis treatment during their second half of pregnancy if they experience fever, contractions, or a decrease in fetal movements [Workowski and Bolan 2015].
Treatment Failure

Definition of syphilis treatment failure: In the absence of potential exposure for reinfection, treatment failure is defined by any of the following [Workowski and Bolan 2015]:

- Persistence or development of new clinical signs or symptoms potentially related to syphilis, such as rashes, ulcers, neurologic/ophthalmic signs or symptoms, or gummas.
- Four-fold increase in nontreponemal serology (e.g., RPR 1:4 increases to 1:16).
- Failure of the nontreponemal serology to decrease 4-fold within 12 to 24 months of treatment.

Treatment failure has been reported in patients with HIV at all stages of syphilis, and with all of the recommended regimens. Consultation with a provider experienced in the management of STIs is indicated when a person with HIV experiences syphilis treatment failure. The NYSDOH Clinical Education Initiative Line (866-637-2342) enables clinicians in NYS to discuss PEP, PrEP, HIV, HCV, and STI management with a specialist, and the New York City STD/HIV Prevention Training Center provides HIV-related educational resources and training for providers. Syphilis treatment failure is distinguished from rising titers that are reflective of reinfection. The use of antiretroviral therapy to restore immune function may reduce treatment failure rates in patients with HIV and syphilis [Ghanem, et al. 2008].

Sex and Needle-Sharing Partner Exposure to Syphilis and HIV

RECOMMENDATIONS

New York State Requirements

- New York State (NYS) Public Health law requires that clinicians report all suspected or confirmed syphilis and HIV diagnoses to the local health department in the area where the patient resides.
  - See NYSDOH Communicable Disease Reporting Requirements
- NYS Public Health Law requires that medical providers talk with HIV-infected individuals about their options for informing their sex and needle-sharing partners that they may have been exposed to HIV and syphilis, including the free, confidential partner notification assistance offered by NYSDOH and New York City Department of Health and Mental Hygiene (NYC DOHMH).
  - See NYSDOH Information on Partner Services and NYC DOHMH Contact Notification Assistance Program (CNAP) for STI/HIV partner notification assistance.

Exposed Sex and Needle-Sharing Partners

- Clinicians should test and treat patients who report exposure to syphilis according to the recommendations in Table 5: Standard Testing and Treatment of Sex Partners Exposed to Syphilis. (A2)
- When a patient with HIV is diagnosed with syphilis, clinicians should advise the patient to encourage sex and needle-sharing partners to seek medical care for possible exposure to both HIV and syphilis. (A3)

Sexual transmission of *T. pallidum* occurs in the presence of mucocutaneous syphilitic lesions. These lesions are uncommon after the first year of infection [Workowski and Bolan 2015].

Presentation of a new sexually transmitted infection (STI) in a patient with HIV suggests sex partner exposure to both HIV and the STI. Clinicians should inform patients that any sex or needle-sharing partner who does not have confirmed HIV infection should have routine HIV testing for early identification of HIV acquisition. If a patient with an HIV exposure presents within 36 hours, evaluation for non-occupational post-exposure prophylaxis should occur. When possible, onsite availability of HIV testing and STI treatment for partners is ideal because it may increase the likelihood that partners will receive timely access to HIV testing and appropriate treatment, including HIV post-exposure prophylaxis and treatment for the STI as needed (see the NYSDOH AI guideline PEP for Non-Occupational Exposure to HIV). Such strategies may also
increase identification of individuals who require ongoing medical care. Partner education about reducing high-risk behaviors, including counseling about the use of barriers, such as male and female condoms, and making condoms visibly available in the clinic, may further decrease the risk of transmission of both HIV and other STIs. Patient education about Undetectable=Untransmittable (U=U) as an HIV prevention strategy should stress that an undetectable HIV viral load prevents only the sexual transmission of HIV. Consistent and correct condom use remains the best method for preventing pregnancy and the transmission of STIs other than HIV. Data are lacking to determine whether U=U prevents HIV transmission through needle sharing.

The NYSDOH Partner Services program provides assistance to individuals with HIV and to care providers who would like help notifying a patient’s sex partner(s) of possible exposure to HIV, chlamydia, gonorrhea, or syphilis. Available options for partner notification include anonymous notification from the local health department, dual disclosure (patient disclosure with the help of Partner Services staff), and self-disclosure. Partner Services staff within local health departments work with patients to develop a plan to notify their partners, whether that plan includes staff notifying potentially exposed partners anonymously or helping patients who choose to tell their partners on their own develop a notification plan and strategy [CDC 2017a].

The local health department will confidentially notify sex partners exposed to syphilis about the need for clinical and serological evaluation and for treatment if they are diagnosed with syphilis. Standard testing and treatment for exposed sex partners is described in Table 5: Standard Testing and Treatment of Sex Partners Exposed to Syphilis, below. Long-term sex partners of patients diagnosed with latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of findings.

→ KEY POINTS

- When a patient with HIV is diagnosed with syphilis, the clinician should inform the patient about the implications of the diagnosis for his/her sex partner(s):
  - A new STI diagnosis signals that the patient was engaging in sexual behaviors that place sex partners at increased risk of acquiring HIV infection.
  - A sex partner may also have been exposed to syphilis and should be tested and evaluated for treatment.
  - The local health department may contact a sex partner confidentially about the potential exposure and treatment options.
- Clinicians should provide patients with information and counseling about notifying partners, risk reduction, and safer sex practices.

<table>
<thead>
<tr>
<th>Timing of Partner Exposure</th>
<th>Testing</th>
<th>Treatment (Rating)</th>
<th>Key Points</th>
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| Within 90 days of the patient’s diagnosis of primary, secondary, or early latent syphilis | Baseline testing | Presumptive [b] (A2) | • After initial infection, the incubation period of syphilis can last from 3 weeks to 3 months; therefore, sex partners who were exposed within 90 days of a patient’s diagnosis of primary, secondary, or early latent syphilis may be infected (incubating infection) even if their serologic syphilis test is nonreactive.  
  • Sex partners who were exposed within 90 days of a patient’s diagnosis of primary, secondary, or early latent syphilis should receive presumptive treatment. |
| >90 days before a patient’s diagnosis of primary, secondary, or early latent syphilis | Baseline testing | Based on test results (A3) | • Sex partners may be treated presumptively [b] if serologic test results are not available immediately and the opportunity for follow-up is unlikely. |

a. Adapted from Centers for Disease Control and Prevention [Workowski and Bolan 2015].

b. Baseline syphilis testing of sex partners treated presumptively should still be performed to ensure that, if positive, other individuals who may have been exposed are notified and treated.
References


NYSDOH unpublished data.


All Recommendations

☑ All RECOMMENDATIONS: Management of Syphilis in Patients with HIV

Transmission and Prevention

- Clinicians should inform patients with HIV about the risk of acquiring syphilis and other sexually transmitted infections (STIs) from close physical contact with all sites of possible exposure, including the anus, cervix, vagina, urethra, tongue, oropharynx, or any other location where infectious lesions may be present. (A3)

Patient Education

- When patients with HIV are diagnosed with early syphilis (primary, secondary, or early latent stage), clinicians should educate patients about the following:
  - Risk-reduction strategies, including the value of condom use (A2)
  - The potential for oral transmission of syphilis (A3),
  - The benefits of identifying infection early (A3), and
  - The need for prompt evaluation and therapy for sex partners (A3).

Serologic Screening

- Clinicians should obtain serologic screening for syphilis at least annually for all patients with HIV (see Table 2: Screening and Diagnostic Tests for Syphilis and Table 3: Interpretation of Results of Reverse-Sequence Testing for Syphilis). (A2)
- In response to the current epidemiology in NYS, clinicians should perform syphilis screening every 3 months (A3) for HIV-infected men who have sex with men (MSM) at highest risk of syphilis infection, including those who:
  - Report, or whose partners report, multiple or anonymous sex partners. (A3)
  - Have been, or whose sex partners have been, diagnosed with or treated for a bacterial sexually transmitted infection (STI) since the last evaluation. (A3)
  - Engage, or whose sex partners may engage, in sexual activity at sex parties or other high-risk venues. (A3)
  - Are involved, or whose sex partners may be involved, in transactional sex (e.g., sex workers and their clients). (A3)
  - Report recreational substance use during sexual activity. (A3)
  - Self-identify as at high risk of STIs. (A3)

Screening in Pregnancy

- Clinicians should obtain serologic screening for syphilis for pregnant patients with HIV at the first prenatal visit, during the third trimester (28-32 weeks of gestation), and at delivery. (A2)

Sexual History

- Clinicians should ask all patients about sexual behaviors and new sex partners at each routine monitoring visit to assess for risk behaviors that require repeat or ongoing screening. (A3)

Presentation and Diagnosis

- As part of the initial and then annual comprehensive physical examination for patients with HIV, clinicians should examine all skin and mucosal surfaces for lesions, especially less-visible areas, such as the anus, cervix, vagina, vulva, urethra, oropharynx, and under the foreskin in uncircumcised males. (A3)
- Clinicians should perform a neurologic review of systems, including ophthalmologic and otic, for all patients with HIV who are diagnosed with syphilis and follow up with further neurologic evaluation, as recommended in Table 4. Recommended Treatment and Follow-Up of Syphilis in Patients with HIV. (A2)
Clinicians should ensure that two-stage syphilis testing is performed by the laboratory if the initial screen is reactive. (A1)

Clinicians should perform a nontreponemal test, such as the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) test, for repeat screening in patients who have a history of syphilis infection. (A1)

Clinicians should perform gonorrheal and chlamydial testing for any patient with HIV who is diagnosed with syphilis infection. (A2)

Clinicians should include neurosyphilis in the differential diagnosis of all patients with HIV who present with neurologic, ophthalmologic, otic, or neuropsychiatric signs or symptoms. (A2)

Clinicians should perform a lumbar puncture in patients with HIV who have syphilis or a history of syphilis when patients present with the following:
- Neurologic, ophthalmologic, otic, or neuropsychiatric signs or symptoms that are not explained by another etiology. (A2)
- Evidence of treatment failure (see Treatment Failure in the Treatment and Follow-Up section of this guideline). (A2)
- Evidence of active tertiary syphilis (aortitis, gummas). (A3)

Reporting: New York State Requirement

Clinicians must report all suspected or confirmed syphilis diagnoses to the local health department of the area where the patient resides according to NYS requirements.

- See NYSDOH Communicable Disease Reporting and NYC Health Reporting Diseases and Conditions.

Treatment

Because of the possibility of false-negative test results in primary syphilis, clinicians should presumptively treat patients at risk of syphilis who present with a lesion typical of a syphilitic chancre. (A3)

Clinicians should use long-acting benzathine penicillin G as the recommended treatment for syphilis in patients with HIV. (A2)
- See Table 4: Recommended Treatment and Follow-Up of Syphilis in Patients with HIV for dose and frequency according to stage of syphilis.

Clinicians should use only penicillin to treat all stages of syphilis in pregnant patients. (A2)

Clinicians should obtain baseline and monthly assessment of serum nontreponemal reagin levels when treating syphilis in pregnant patients with HIV if the risk of syphilis reinfection is high. (A3)

Treatment in Penicillin-Allergic Patients

Clinicians should administer desensitization therapy followed by penicillin therapy to treat penicillin-allergic patients who have neurosyphilis, other forms of tertiary syphilis, syphilis in pregnancy, or syphilis that cannot be treated by an alternative regimen. (A2)

Clinicians should administer desensitization therapy for patients with HIV, followed by penicillin therapy, rather than attempt alternate therapies if adherence to therapy or close follow-up cannot be ensured. (A3)

Clinicians should not prescribe azithromycin to treat syphilis in patients with HIV. (A2)

Jarisch-Herxheimer Reaction

In women treated for syphilis infection during the second half of their pregnancy, clinicians should
- Obtain a fetal sonogram to evaluate for congenital syphilis. (A2)
- Advise women who experience fever, contractions, or a decrease in fetal movements to seek immediate obstetric care. (A2)

Treatment Failure

Clinicians should perform CSF examination for patients who experience treatment failure, and:
- Initiate parenteral therapy using a recommended penicillin regimen for late latent syphilis if CSF test results are negative. (A2)
- Treat using a recommended penicillin regimen for neurosyphilis if CSF test results are positive. (A2)
New York State Requirements

- New York State (NYS) Public Health law requires that clinicians report all suspected or confirmed syphilis and HIV diagnoses to the local health department in the area where the patient resides.
  - See NYSDOH Communicable Disease Reporting Requirements
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