Syphilis

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Module 2: Self-Study Lessons
Lesson 3: Syphilis

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Introduction

Syphilis is a systemic infection caused by *Treponema pallidum*, a spirochete bacterium that is transmitted primarily through sexual activity or vertical transmission during pregnancy. Cases of syphilis, including congenital syphilis, have risen substantially in recent years in the United States. In the absence of treatment, persons who acquire *T. pallidum* remain chronically infected and can develop an array of clinical manifestations. Syphilis characteristically progresses in stages (primary, secondary, latent, and tertiary), with episodes of active clinical disease interrupted by periods of latent infection. Neurosyphilis, ocular syphilis, and/or otosyphilis can occur at any of these stages (Figure 1).[1,2] Without treatment, chronic *T. pallidum* infection can result in significant morbidity, potentially affecting nearly every organ system, and can rarely result in death. In addition, untreated syphilis in women can lead to fetal demise and devastating congenital infection of the neonate. Note: content related to syphilis in pregnancy and congenital syphilis will be addressed in detail in the lesson *Syphilis in Pregnancy and Congenital Syphilis*. This lesson will be posted in the near future.

Epidemiology in the United States

2023 Syphilis Surveillance Data

Although surveillance reporting of syphilis cases includes data for multiple syphilis stages, the reported cases for primary and secondary syphilis most accurately represent new infections. During the past 80 years in the United States, the incidence of syphilis has fluctuated, but since the year 2000, the reported number of syphilis cases in the United States has increased, with a leveling off in 2023.[3] In 2023, the total number of reported cases of syphilis (all stages and congenital) was 209,253, including 53,007 cases of primary and secondary syphilis.[3] In the previous year (from 2022 to 2023), the number of reported total syphilis cases increased by 1%, but the number of primary and secondary syphilis ases decreased by 10%.[3] The figure and text below summarize several key epidemiologic features of syphilis in the United States, as reported for the year 2023 (Figure 2).[3]

- **Sex**: The rate of reported primary and secondary syphilis cases in 2023 among men (23.6 cases per 100,000 males) was 2.9-fold higher than among women (8.1 cases per 100,000 women). For both males and females, rates of reported primary and secondary syphilis increased from 2013 to 2022, but decreased from 2022 to 2023.
- **Sex Partner**: Men who have sex with men (MSM) accounted for approximately one-third (32.7%) of reported cases of primary and secondary syphilis and more than half (57.5%) of reported cases were among men (when the sex of the partner was known). From 2022 to 2023, the number of reported cases of primary and secondary syphilis among men who have sex with men decreased by 13%, which was the first year of decline in more than 15 years.
- **Age**: The highest rates of reported primary and secondary cases of syphilis in both males and females occurred in persons 25 to 34 years of age.
- **Race/Ethnicity**: For both males and females, the rate of primary and secondary syphilis was highest among American Indian/Alaska Native individuals and second highest among Black/African American persons.
- **Geographic Region**: The reported rate of syphilis infection for all stages was highest in the West (75.3 per 100,000 persons), closely followed next by the South (74.0 per 100,000 persons). The five states with the highest rates of syphilis infection (all stages) were South Dakota, New Mexico, Mississippi, Arizona, and Nevada.
- **HIV Coinfection**: In cases of primary and secondary syphilis when the HIV status of the person diagnosed was known, HIV coinfection was present in 41.0% of MSM, in 6.5% of men who have sex only with women, and in 4.1% of women.[Q] Syphilis Epidemiology

Factors Associated with Syphilis Diagnosis and Risk for HIV Acquisition

Persons with the highest rates of syphilis include MSM and individuals with HIV.[3,4,5] Additional factors associated with an increased rate of syphilis include a history of incarceration, methamphetamine use, injection drug use, and exchanging sex for money or drugs.[3,5,6,7] Among MSM, the use of methamphetamine has been associated with a substantially increased risk of acquiring syphilis.[6] In addition, among MSM who do not have HIV, a diagnosis of primary or secondary syphilis is associated with a significantly increased risk of subsequently acquiring HIV.[8,9,10]

Microbiology, Pathogenesis, and Transmission

Organism and Classification

The etiologic agent in syphilis is *Treponema pallidum*—from the Greek terms trepo (“to turn”) and nema (“thread”) and the Latin term pallida (“pale”) (Figure 3).[11] *Treponema pallidum* belongs to the spirochete class and is a corkscrew-shaped, motile microaerophilic bacterium that cannot be viewed by normal light microscopy. Isolation of *T*. *pallidum* was first performed using a live rabbit-model in vivo system, but subsequently, successful cultivation and propagation of *T*. *pallium* has been achieved using in vitro tissue culture.[12,13,14] This spirochete bacterium is thin (0.1 to 0.18 micrometers in diameter) and 6 to 20 micrometers in length.[15] *Treponema pallidum* has been erroneously described as a gram-negative bacterium, but this organism lacks lipopolysaccharide (LPS), a hallmark of gram-negative organisms.[16][Q] Biology of Treponema pallidum

Transmission

The major routes of transmission for *T*. *pallidum* are sexual (during the primary and secondary stages of syphilis) and hematogenous (in utero via transplacental spread to a fetus).[17] During sexual transmission, *T*. *pallidum* enters the body via skin and mucous membranes through macroscopic and microscopic abrasions during sexual contact.[16] Persons who acquire *T*. *pallidum* are contagious to their sex partners throughout the primary and secondary stages of infection (when lesions or rash are present).[16,18] Some patients may be asymptomatic and diagnosed with latent syphilis, but may have more subtle undetected manifestations, such as a small localized rash or mucosal lesions that are not visible, such as lesions in the anal canal. Although sexual transmission of *T*. *pallidum* usually results from contact with genital mucosal membranes, it can also occur at other sites, including the mouth, anorectal areas, and cutaneous lesions. Maternal transmission predominantly occurs via transplacental passage of *T*. *pallidum* during maternal spirochetemia; less often, transmission can occur if the newborn has contact with maternal genital lesions at the time of delivery.[16,19] In contrast to sexual transmission of syphilis, which nearly always occurs in the early stages of syphilis, vertical transmission can occur during any stage of syphilis. Other forms of hematogenous transmission of *T*. *pallidum* are rare: transfusion-associated syphilis has been virtually eliminated in the United States, and transmission through needle-sharing with injection drug use is infrequent.[17] [Q] Transmission of Treponema pallidum

Clinical Manifestations

Syphilis has often been called “the great imitator” because so many of the signs and symptoms may be difficult to differentiate from those of other diseases.[17,20,21,22] Early after infection, before clinical signs or symptoms appear, *T. pallidum* can spread to the circulatory system, the lymphatic system, regional lymph nodes, and the central nervous system. Early clinical manifestations (primary and secondary stages) predominantly involve the skin and mucosal surfaces, although secondary syphilis may be accompanied by systemic manifestations.[17,23] Latent disease has no clinical signs or symptoms, but late manifestations (seen after years of infection) may affect virtually any organ system. Neurosyphilis, ocular syphilis, and otosyphilis can occur at any stage of infection. Obtaining a detailed history is critical for determining the duration of infection and assessing possible reinfection. Assessment should include the following:

- A history of syphilis (if yes, obtain results of previous serologic tests for comparison)
- Known contact with someone with primary, secondary, or early latent syphilis
- Signs or symptoms of syphilis in the past 12 months

Primary Syphilis

Following the inoculation of *T. pallidum* at the entry site, organisms proliferate, sensitize lymphocytes, and activate macrophages, causing the formation of a primary lesion or “chancre” at the site of inoculation.[18] If clinically evident, the chancre appears about 2 to 3 weeks (range 10 to 90 days) after the acquisition of *T. pallidum*.[2,17] Chancres progress from a papule to an ulcer, which is typically painless, round to oval, indurated, well-circumscribed, with a clean base and heaped-up margins.[1] Less often, individuals with primary syphilis may develop multiple painful anogenital lesions.[24] The most common sites where chancres develop include the oral region, penis, labia, or perianal region (Figure 4).[1,17] Regional firm lymphadenopathy often develops in proximity to primary syphilitic lesions.[25,26] Syphilitic chancres are highly infectious and heal spontaneously (without treatment) in approximately 3 to 8 weeks.[2,17] If untreated, persons with primary syphilis may subsequently develop other manifestations of syphilis. Evaluation of any sexually active persons with a genital or perianal ulcer should include testing for syphilis and genital herpes.[27]

Secondary Syphilis

Secondary lesions reflect hematogenous dissemination of *T. pallidum* and generally appear 4 to 10 weeks after the onset of the primary chancre.[2] In fewer than 10% of cases, primary and secondary stages may overlap.[17] Signs and symptoms of secondary syphilis are often the first observed clinical manifestation of syphilis, as primary lesions are often overlooked or not recognized.[17] Relapses of secondary symptoms occur in up to 25% of untreated persons.[2] A wide array of manifestations can occur with secondary syphilis (Figure 5):[1,22]

- **Generalized Body Rash**: A generalized body rash occurs in more than 75% of persons with secondary syphilis and is usually nonpruritic. The red or copper-colored lesions are typically 1 to 2 cm in size and can appear as any combination of macular, papular, squamous, or pustular forms. The rash characteristically involves the chest, back, palms, and soles.
- **Lymphadenopathy**: Approximately 50 to 86% of persons with secondary syphilis develop lymphadenopathy, which may be diffuse.
- **Systemic Symptoms**: Patients often present with malaise, fever, and other nonspecific constitutional symptoms.
- **Mucous Patches**: The development of mucous patches occurs in 6 to 30% of patients and manifests as flat patches located in the oral cavity, pharynx, larynx, or genital region.
- **Condylomata Lata**: Approximately 10 to 20% of persons with secondary syphilis will have condylomata lata lesions, which appear as moist, heaped-up, wart-like papules in warm, intertriginous areas (most commonly gluteal folds, perineum, and perianal), these lesions are highly contagious.

- **Alopecia**: About 5% of patients develop patchy alopecia, most often in the occipital or bitemporal scalp region, but some patients will have loss of the lateral region of the eyebrows.
- **Visceral Organ Involvement**: In some cases, syphilis may involve one or more visceral organs, including the liver, kidney, lungs, gastrointestinal tract, and spleen. The most common visceral organ manifestations are nephritis and hepatitis (with a high alkaline phosphatase level).[Q] Condylomata Lata

Latent Syphilis

Latent syphilis is a stage of syphilis characterized by the persistence of *T. pallidum* organisms in the body without causing signs or symptoms. Periods of clinical latency may occur between the primary and secondary stages, between secondary relapses, and after the secondary stage. The diagnosis of latent syphilis is made when an individual has (1) seroreactivity indicating infection with *T. pallidum*, (2) no past diagnosis of syphilis, and (3) no active manifestations of syphilis.[28] Latent syphilis is classified into early latent and late latent.[28,29] When evaluating an individual with latent syphilis, the health care provider should inquire about prior symptoms of primary or secondary syphilis, determine whether sexual contact occurred with a partner with primary or secondary syphilis within the past year, perform an examination to look for syphilis-related manifestations, and review all prior syphilis serologic test results.

- **Early Latent Syphilis (Infection of Less than 1 Year in Duration)**: Persons with latent syphilis are classified in the subcategory of early latent syphilis if they have no clinical signs or symptoms of syphilis and ANY of the following:[28]
    - A documented seroconversion within the prior 12 months
    - A sustained (longer than 2 weeks) fourfold or greater increase in the titer in the prior 12 months in a person previously treated for syphilis
    - Unequivocal symptoms of primary or secondary syphilis within the prior 12 months
    - Contact in the prior 12 months with a sex partner who had untreated primary, secondary, or early latent syphilis
    - Documented reactive nontreponemal and treponemal tests, and the only possible exposure occurred during the previous 12 months
- **Late Latent or Latent Unknown Duration Syphilis (Infection Greater than 1 Year in Duration)**: Persons are considered to have late latent syphilis (or syphilis of unknown duration) if they meet ALL the following criteria:[28]
    - A reactive nontreponemal and treponemal test and no past diagnosis of syphilis
    - No clinical manifestations of syphilis
    - They do not meet criteria for early latent syphilis [Q] Classification of Latent Syphilis

Tertiary Syphilis

Tertiary syphilis is rare because of the widespread availability of antibiotics, enhanced screening for syphilis, and treatment for early syphilis. Without treatment, however, approximately 30% will progress to the tertiary stage 2 to 50 years after the original infection.[1] Tertiary syphilis can manifest as gummatous disease, cardiovascular syphilis, late neurosyphilis, ocular syphilis, or otic syphilis.[1]

- **Gummatous Disease**: The term gummatous syphilis (late benign syphilis) refers to a reactive granulomatous process that may develop in any tissue and may cause symptoms directly from a mass effect or local inflammation.[1,17] Histologic findings typically consist of granulomas with aggregates of plasma cells and multinucleated giant cells, often with central necrosis. The most common sites are skin, bones, and liver.
- **Cardiovascular Syphilis**: Persons with cardiovascular syphilis most often have pathologic lesions of the aortic vasa vasorum, which can manifest as an ascending aortic aneurysm, aortic valve insufficiency, myocarditis, and/or coronary artery stenosis.[1,17]
- **Late Neurosyphilis**: Manifestations of tertiary (late) neurosyphilis are categorized as

meningovascular disease or parenchymatous forms (general paresis and tabes dorsalis). If meningovascular syphilis occurs, it typically manifests 5–12 years after initial infection, whereas general paresis and tabes dorsalis occur later (typically more than 15 years after initial infection).[1] Manifestations of meningovascular syphilis may include seizures, hemiplegia, aphasia, and spinal vascular disease.[1] General paresis can manifest as cognitive impairment, personality changes, and/or psychiatric changes (emotional lability, delusions, paranoia).[1] Patients with tabes dorsalis can have sensory ataxia, weakness, paresthesia (lightning pain), bladder dysfunction, rectal incontinence, and visceral instability.

- **Ocular and Otic Syphilis**: Tertiary syphilis manifesting as late ocular or otic syphilis is a very rare manifestation of tertiary syphilis.[1] Ocular findings can include impaired reactive response to light stimuli (Argyll Robertson pupil).

Neurosyphilis

Neurosyphilis occurs when *T. pallidum* invades the central nervous system, and this may occur at any stage of syphilis; neurosyphilis is categorized as early neurosyphilis and late neurosyphilis.[2,30] Ocular and otic involvement can occur with early or late infection.[1]

- **Early Neurosyphilis**: Cerebrospinal fluid (CSF) abnormalities can occur in 50 to 60% of persons with early syphilis and are of unknown significance in the absence of neurologic signs or symptoms.[31,32] Meningeal syphilis is the most common manifestation of early neurosyphilis, and it typically occurs weeks to months (and almost always within a year) after initial infection.[30] Symptomatic syphilitic meningitis often resembles aseptic meningitis, and symptoms may include fever, headache, and stiff neck; with basilar involvement, cranial nerve abnormalities can develop, particularly cranial nerves II, VI, and VIII.[30] Meningovascular syphilis typically develops 5 to 12 years after initial infection, but it can occur earlier. Meningovascular syphilis, which results from *T. pallidum* infection and inflammation of small and medium central nervous system blood vessels, most often manifests as a stroke-like syndrome with seizures.[33]
- **Late Neurosyphilis**: Late forms of neurosyphilis usually occur multiple years or even decades (typically at least 15 years) after infection.[1,30] In the modern era, this type of neurosyphilis is rarely seen. Clinical manifestations include general paresis and tabes dorsalis but can present with a wide variety of neurologic symptoms, including dementia.[2,30]

[Q] Manifestations of Neurosyphilis_

Ocular Syphilis

Since *T. pallidum* can potentially infect any part of the eye, a broad range of symptoms and manifestations associated with ocular syphilis may occur with or without neurosyphilis.[34,35,36,37] Ocular syphilis can develop at any stage of syphilis and can cause acute or chronic symptoms; most often, this occurs in the early stages of syphilis.[28,35] Although ocular syphilis can involve virtually any region of the eye, the most common clinical presentation is uveitis—anterior, posterior, or panuveitis (Figure 6).[34,35,38] Other described manifestations include lid involvement, episcleritis, vitritis, papillitis, interstitial keratitis, retinitis, and optic neuritis.[35] The clinical presentation of ocular syphilis can have significant overlap with other infectious and noninfectious eye diseases. Persons with syphilis who have ocular complaints should have a complete cranial nerve evaluation and receive a referral to an ophthalmologist for an immediate evaluation.[28] In addition, if any cranial nerve abnormalities are present, a lumbar puncture should be performed with cerebrospinal fluid analysis to determine if concomitant neurosyphilis is present.[28] In the absence of any neurologic manifestations, lumbar puncture is not indicated.[28] [Q] Ocular Syphilis

Otosyphilis

Otic involvement from *T. pallidum* infection can occur at any stage of syphilis, and persons with otosyphilis

usually present with hearing loss, tinnitus, vertigo, or a combination of these manifestations.[39,40] Hearing loss with otosyphilis is typically sensorineural and can involve one or both ears.[39,40] Otosyphilis can develop at any stage of syphilis and can cause acute or chronic symptoms; most often, this occurs in the early stages of syphilis.[28] Otosyphilis can develop with other syphilis manifestations, including neurosyphilis or ocular syphilis. Thus, individuals with suspected or diagnosed otosyphilis should undergo an initial screening evaluation for neurosyphilis and ocular syphilis.[40] Persons with a suspected diagnosis of otosyphilis should receive a referral for an immediate auditory examination by an otolaryngologist or audiologist.[28] Individuals with a positive serologic test for syphilis who have isolated auditory symptoms and a normal neurologic examination do not require lumbar puncture with cerebrospinal fluid examination.[28]

Early, Non-Primary, Non-Secondary Syphilis

For the United States STI surveillance purposes, the CDC utilizes a category that is referred to as “early, non-primary, non-secondary syphilis”. Conceptually, this is meant to capture a syphilis diagnosis and reporting of all persons who acquired syphilis in the last year, but without manifestations of primary or secondary syphilis. This would include those who had clearly documented infection within the past 12 months and (1) were asymptomatic (latent syphilis) *or* (2) had syphilis-related manifestations (e.g., ocular syphilis, otosyphilis, and/or neurosyphilis) without manifestations of primary or secondary syphilis.

- **Example 1**: A person is receiving HIV preexposure prophylaxis (PrEP) and is undergoing regular syphilis screening. This person has a new positive syphilis serologic test (most recent testing 3 months ago was negative). The individual reports no current or recent (past 6 months) syphilis-related clinical manifestations. This person is diagnosed with early latent syphilis and, for reporting purposes, would be in the stage/category of early non-primary, non-secondary.
- **Example 2**: A person presents with a 2-day history of ocular symptoms and serologic testing for syphilis is positive. Recent serologic syphilis testing 4 months prior was negative. This person has no other syphilis-related clinical manifestations. This individual was diagnosed with ocular syphilis. Because they have syphilis-related manifestations, the use of the term latent syphilis is not appropriate. The infection is considered early since syphilis serologic testing 4 months earlier was negative. This person would be considered to have ocular syphilis and, for reporting purposes, would be in the stage/category of early, non-primary, non-secondary.

Laboratory Diagnostic Tests

The laboratory diagnosis of syphilis is challenging and requires using a combination of clinical and laboratory criteria to differentiate active infection, prior infection, and absence of infection.[41,42,43] Serologic testing remains the primary tool for diagnosis in most patients with syphilis, and these tests include nontreponemal and treponemal tests.[43,44,45] Although *T. pallidum* has been cultivated in research laboratories, sending samples for culture for routine clinical practice is not an option. The following summarizes the different test types used for diagnosing syphilis. All persons diagnosed with syphilis should also have HIV testing, unless they already have a known HIV diagnosis.

Direct Detection of *Treponema pallidum*

Dark-Field Microscopy

Dark-field microscopy of lesion exudate or tissue is a definitive method for making an immediate diagnosis of primary or secondary syphilis.[28,42] *Treponema pallidum* cannot be viewed by normal light microscopy. Dark-field microscopy can identify *T. pallidum* with its spiral shape, length of 6 to 20 micrometers, and corkscrew motion (Figure 7).[46] Dark-field microscopy is infrequently used in clinical practice because most facilities do not have a dark-field microscope, and most clinicians do not know how to appropriately obtain specimens. The specificity of dark-field microscopy with oral specimens is extremely poor due to the abundant non-syphilitic oral *Treponema* species.

Polymerase Chain Reaction

Although polymerase chain reaction (PCR) testing is sometimes used for research purposes and locally developed and validated by some laboratories, there is no FDA-approved PCR test for syphilis at present.

Direct Fluorescent Antibody Test

The direct fluorescent antibody (DFA) test can detect *T. pallidum* antigens in tissue samples. The test uses antibodies specific to pathogenic treponemes and can generally identify *T. pallidum* in oral or rectal lesions, even with the presence of background nonpathogenic spirochetes.[41]

Tissue Staining

Silver staining and immunohistochemical staining of tissue samples can demonstrate characteristic spirochetes on clinical biopsy specimens.[42]

Serologic Testing for Syphilis

Serologic testing for syphilis involves the use of two types of serologic tests: treponemal and nontreponemal.[43,44] Use of only one type of serologic test is not sufficient for making a diagnosis of syphilis, since each test used alone has major limitations, including false-positive results in persons without syphilis and the inability of treponemal tests to distinguish between recent and distant infection.[43,47] Note that persons with a prior history of syphilis usually maintain a positive treponemal (antibody) test for life. Therefore, individuals with a prior history of syphilis generally require rescreening using a nontreponemal test ((Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR]).[43] In addition, false-negative syphilis serologic tests can occur among persons with primary syphilis due to absent or very low levels of antitreponemal antibodies very early after infection.[43]

Treponemal Serologic Tests (EIA, CIA, TP-PA, FTA-ABS)

The treponemal serologic tests include various enzyme immunoassays (EIAs) and chemiluminescence immunoassays (CIAs), as well as the *T. pallidum* particle agglutination (TP-PA) and fluorescent treponemal

antibody absorption (FTA-ABS) tests.[42,43] These tests measure antibodies directed against *T. pallidum* antigens by enzyme immunoassay immunofluorescence (Figure 8) or particle agglutination; most detect IgG only, whereas some detect both IgM and IgG. For initial screening for syphilis, the EIA or CIA assay is usually the preferred treponemal test to use. All treponemal tests provide a qualitative test result. For persons diagnosed with syphilis, treponemal tests typically remain reactive for life, even after adequate treatment. There are, however, approximately 15 to 25% of persons treated during the primary stage of syphilis who eventually revert to being serologically nonreactive with a treponemal serologic test.[43,48]

Nontreponemal Serologic Tests (RPR, VDRL)

The commonly used nontreponemal tests are the rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) tests.[42,43] The nontreponemal tests (RPR and VDRL), which measure antibodies directed against lipoidal antigens, such as cardiolipin and lecithin, are not specific for *T. pallidum*.[43,49] Reactive RPR or VDRL test results are then reported as a quantitative titer, which typically correlates with disease activity.[28] A fourfold or greater change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference.[44] The nontreponemal tests are labor-intensive to perform, and biologic false-positive tests can occur from multiple causes, including pregnancy, autoimmune diseases, HIV, hepatitis C virus, other treponemal infections, and immunizations.[43,49] For monitoring persons with syphilis, sequential serologic tests should use the same testing method (VDRL or RPR) and preferably in the same laboratory.[43] Further, when evaluating congenital syphilis, the neonate and mother should have the same type of nontreponemal test used for comparison. Several years after effective syphilis treatment, the nontreponemal tests usually become nonreactive (or persist at a very low titer).[44] In addition, some individuals with syphilis will have seroreversion to a negative syphilis test even without syphilis treatment.

Point-of-Care Tests for Syphilis

There are two point-of-care tests authorized by the United States Food and Drug Administration (FDA) for point-of-care syphilis testing: (1) Syphilis Health Check Treponemal Antibody Test (SHC) and (2) ChemBio DPP HIV-Syphilis (ChemBio DPP), which detects HIV as well as syphilis.[50] Both assays typically use whole blood collected from a fingerstick, and require approximately 15 minutes to perform.[50] These tests are treponemal (antibody) tests and have a lower sensitivity and specificity than laboratory-based treponemal tests.[50,51] A positive point-of-care test result should be confirmed by a laboratory-based nontreponemal test and a second treponemal (antibody) test.[50] In addition, if there is a high index of suspicion for a diagnosis of syphilis and the point-of-care syphilis test is negative, further testing with a laboratory-based syphilis test should be performed. The point-of-care HIV-syphilis combination test was evaluated in an emergency department setting and shown to have excellent performance characteristics, high perceived acceptability from patients, and good feasibility for use in this setting.[52]

In-Home Syphilis Antibody Test

In August 2024, the FDA authorized the use of an in-home rapid syphilis test—the NOWDiagnostics First to Know Syphilis Test.[53] This self-test is a treponemal antibody assay that requires a single drop of blood. When compared with traditional laboratory-based syphilis tests, the syphilis self-test has a reported sensitivity of 93.4% and a specificity of 99.5%. This test is performed after collecting a fingerstick blood sample (using a finger lancet), requires 15 minutes to perform, and must be read within 30 minutes. Individuals with a positive self-test require confirmatory testing with laboratory-based syphilis serologic tests. Use of the self-test (an antibody test) is not recommended in persons with a prior diagnosis of syphilis, since most people with syphilis continue to have a positive syphilis antibody test for the remainder of their life, even if treated appropriately.

Performance of Serologic Tests for Syphilis

The common patterns for serologic reactivity with syphilis tests depend on the specific test used, the stage of

syphilis, and whether the person has received treatment for syphilis.[44,45,54] Likewise, the sensitivity of serologic testing also varies based on the test used and the stage of syphilis (Table 1).[41,45] Serologic testing for syphilis has the highest yield for secondary syphilis.

- **False-Positive Reactions**: With both nontreponemal and treponemal serologic tests for syphilis, false-positive reactions can occur; the rate of false-positive tests is significantly higher with nontreponemal tests (RPR or VDRL) than with treponemal (EIA) tests.[43,55] The most common causes of false-positive test results include older age, autoimmune disorders, cardiovascular disease, pregnancy, malaria, leprosy, other spirochete infections, and recent immunizations.[28,56]
- **False-Negative Reactions with Early Syphilis**: Serologic tests for syphilis may be negative during very early primary syphilis, especially with nontreponemal tests (RPR or VDRL), but can also occur with treponemal tests (EIA).[44,54] Thus, when serologic tests do not correspond with clinical findings suggestive of primary syphilis, presumptive treatment is recommended if the person has known risk factors for syphilis. Other tests, such as dark-field microscopy, biopsy, or PCR, can also be considered if available.
- **False-Negative Reaction due to Prozone Effect**: False-negative reactions infrequently occur with nontreponemal testing due to the prozone effect.[43,57] The prozone effect occurs when very high serum antibodies supersaturate the antigens used in the nontreponemal assay, thereby interfering with the antigen-antibody lattice network needed to visualize a flocculation reaction.[57,58] Overall, this occurs in less than 2% of cases of syphilis.[57,59,60] This false-negative reaction is most likely to occur in patients with secondary syphilis and HIV infection. If clinical suspicion of secondary syphilis is high and the nontreponemal testing is negative, the clinician should alert the laboratory of a suspected prozone effect, and the laboratory should reevaluate the clinical sample after diluting the serum, typically a 1/16 dilution.[Q] Prozone Effect

Prior Serologic Testing for Syphilis

The health care professional should determine the date and results of the most recent serologic test for syphilis, even if the person under evaluation reports no history of the disease. For persons who have a prior diagnosis of syphilis, the most recent RPR or VDRL titer is important to compare with a current RPR or VDRL titer. In addition, prior results and treatment history are particularly helpful when evaluating an individual who has a low titer for a nontreponemal serologic test for syphilis, no signs or symptoms that suggest a clinical diagnosis of syphilis, and no known contact with an early case of syphilis. Local health departments may be able to provide information on whether the person has been reported as having had syphilis in the past, including reported serologic test results and treatment history. Information from other jurisdictions (or states) may also be available. Obtaining prior results is important since patients might not be aware of a past diagnosis of syphilis or what treatment they were given.

Serologic Screening Algorithms

The treponemal (EIA and CIA) and nontreponemal (RPR and VDRL) tests each have significant advantages and disadvantages as screening tests, and these lab tests are used together as part of a screening algorithm to maximize the sensitivity and specificity for the detection of syphilis infection. The CDC does not recommend one screening method over the other. Clinicians should be aware of their institution’s chosen method for syphilis serologic testing. The two main serologic testing algorithms laboratories use are traditional sequence screening (starting with a nontreponemal test) and reverse sequence screening (starting with a treponemal test).[43] The major advantage of using treponemal tests (EIA or CIA) for initial screening, compared with nontreponemal tests (RPR or VDRL), is improved detection of early primary infection. Note that persons with a prior history of syphilis usually continue to have a reactive treponemal (antibody) test for life. Therefore, individuals with a prior history of syphilis generally require rescreening using a nontreponemal test (RPR or VDRL).

Initial Screening with Treponemal Test (Reverse Sequence Screening)

Initial screening with a treponemal test (EIAs or CIAs) has historically been referred to as the "reverse sequence screening algorithm" (Figure 9).[43,61]

- **Initial Treponemal Test Nonreactive**: A nonreactive initial treponemal result essentially rules out the diagnosis of syphilis, except for persons with recent *T. pallidum* infection. If the patient is suspected to have primary syphilis and the initial nontreponemal test is nonreactive, treatment for primary syphilis should be administered and the nontreponemal test should be repeated several weeks later.[61]
- **Initial Treponemal Test Reactive**: A reactive initial treponemal test (EIA or CIA) test requires further testing with a nontreponemal test (RPR or VDRL) and almost all laboratories will automatically do this.[28,43,61]
    - Follow-Up Nontreponemal Test Reactive: If the follow-up nontreponemal test is reactive and there is no history of prior treatment for syphilis, then a diagnosis of syphilis is confirmed, and treatment is indicated. If the follow-up nontreponemal test is reactive and there is a history of prior syphilis, then the current titer (RPR or VDRL) must be compared with the most recent titer.
    - Follow-Up Nontreponemal Test Nonreactive: With a reactive initial treponemal test (EIA or CIA) and a nonreactive nontreponemal test (RPR or VDRL) follow-up test, a second different treponemal test (usually TP-PA) should be performed.[43,61] In this situation, the CDC recommends not using FTA-ABS as the second treponemal test, due to lower specificity and more difficulty performing the test.[28,61]
        - Second Treponemal Test Nonreactive: If this second treponemal test is nonreactive, then syphilis is unlikely.
        - Second Treponemal Test Reactive: If the second treponemal test is reactive, then several possible scenarios exist: previously treated syphilis, early syphilis, untreated latent syphilis, or a false-positive test.[43] In this situation, individuals with a prior history of appropriate syphilis treatment do not require further management, unless there has been a known reexposure to syphilis after completing prior syphilis treatment. Those without a prior history of treatment should be offered treatment, typically for late latent syphilis, unless their history or examination indicates a recent exposure or other syphilis-related complications, such as neurologic involvement.[61]

Initial Screening with Nontreponemal Test (Traditional Sequence Screening)

Initial screening with a qualitative nontreponemal test (RPR or VDR) has historically been referred to as the "traditional syphilis screening algorithm" (Figure 10).[16,43]

- **Initial Nontreponemal Test Nonreactive**: Persons who have an initial nonreactive nontreponemal test (RPR or VDRL) are considered unlikely to have syphilis, unless they have early syphilis.[43]
- **Initial Nontreponemal Test Reactive**: If the initial qualitative nontreponemal test (RPR or VDRL) is reactive, the laboratory should automatically perform a quantitative (titer) on the same specimen. In addition, persons with a reactive initial nontreponemal (RPR or VDRL) result should have additional testing with a treponemal test (usually TP-PA).[28,43]
    - Follow-Up Treponemal Test Reactive: If the follow-up treponemal test is reactive, then a diagnosis of syphilis is confirmed.
    - Follow-Up Treponemal Test Nonreactive: If the follow-up treponemal test is nonreactive, then a diagnosis of syphilis is unlikely, and the reactive nontreponemal test may represent a biologic false-positive test result.

Screening for New Infection if Previously Treated for Syphilis

For persons previously successfully treated for syphilis, nontreponemal tests (RPR or VDRL) should be used to screen for new *T. pallidum* infection, since treponemal screening tests (CIA or EIA) are antibody-based tests and typically remain reactive for life.[43] In addition, the nontreponemal tests (RPR or VDRL) provide a

quantitative nontreponemal titer that can be compared with prior nontreponemal titers.[43] Ideally, the same type of nontreponemal test (RPR or VDRL) is used when comparing current titers with prior titers, since methods used with the RPR and VDRL are different.[28,43] To make a new laboratory diagnosis of syphilis in a person previously diagnosed with syphilis, the nontreponemal test titer must be at least 4-fold higher than the most recent prior nontreponemal test (using the same type of nontreponemal test).[28,43]

Laboratory Evaluation for Neurosyphilis

All persons with a positive serologic test for syphilis and any new neurologic signs or symptoms should have a lumbar puncture with cerebrospinal fluid (CSF) analysis.[28,43] Persons with ocular syphilis or otosyphilis do not require CSF examination, unless they have concomitant neurologic symptoms or signs.[28] The laboratory diagnosis of neurosyphilis should take into account the CSF white blood cell count, CSF protein (in persons without HIV), and CSF VDRL.[28,43] An elevated CSF white blood cell count (cutoff greater than 5 cells/mm^3 in persons without HIV) and elevated CSF protein can support the diagnosis of neurosyphilis, but are not diagnostic.[62] The CSF VDRL has high specificity, but the sensitivity is low; the CSF RPR is not recommended for the evaluation of neurosyphilis.[28,30,63] The diagnosis of neurosyphilis is considered highly likely if a person has the following three findings: a positive serologic test, neurologic clinical manifestations, and a positive CSF VDRL (in the absence of blood contamination of the CSF). Because of the low sensitivity of CSF VDRL, when this test is negative and a person has suspected neurosyphilis, additional testing should occur with a CSF treponemal test (FTA-ABS).[43,62,64] Persons who have a low pretest probability for neurosyphilis and a negative CSF FTA-ABS (or CSF TP-PA) are unlikely to have neurosyphilis.[28,43]

Diagnosis of Syphilis in Persons with HIV

In general, the clinical course and diagnostic evaluation of syphilis in persons with HIV is similar to that in persons without HIV.[28] Although not common, unusual serologic responses among persons with HIV can occur. If the clinical suspicion of syphilis is high and the serologic tests for syphilis are negative, then the use of other tests (e.g., biopsy of the lesion or rash) and empiric treatment should be considered. In this situation, serologic syphilis tests can also be repeated in 2–4 weeks. Conventional therapy is usually effective. Several studies have shown that CSF abnormalities (mononuclear pleocytosis and elevated protein) are more common in persons with HIV who have a CD4 count of 350 cells/mm^3 or less and/or a nontreponemal serologic test titer of greater than or equal to 1:32.[28] For persons with HIV, a lumbar puncture with CSF examination should be reserved for those with neurologic manifestations.[28] Since persons with HIV may have slight elevations in CSF white blood cell counts at baseline, some experts suggest using a higher cutoff (white blood cell count greater than 10 cells/mm^3) to improve the specificity of this test as a component of the neurosyphilis diagnosis; using a higher cutoff of 20 cells/mm^3 for people with HIV is recommended by some experts to further enhance the specificity, but it does reduce the sensitivity.[62] In addition, CSF protein is not typically used for diagnosing neurosyphilis in persons with HIV, particularly in persons who have a CD4 count of less than 350 cells/mm^3.

Reporting Requirements

Laws and regulations in all states require clinicians, laboratories, or both to report persons diagnosed with syphilis (including congenital syphilis) to a local public health department. Reporting can be done by medical providers, laboratories, or both. Public health can help guide providers in management decisions, as well as to ensure appropriate treatment and follow-up for sex partners.

Screening for Syphilis

In the United States, the main recommendations for syphilis screening are from the 2021 STI Treatment Guidelines and the 2016 U.S. Preventive Services Task Force (USPSTF) Recommendation Statement on Screening for Syphilis Infection in Nonpregnant Adults and Adolescents.[5,28] These recommendations both identify MSM and persons with HIV as high-priority groups for routine syphilis screening.[5,65,66] The following summarizes syphilis screening recommendations in the 2021 STI Treatment Guidelines and [Guidelines] Doxy PEP Guidelines.[28,66,67]

Men and Nonpregnant Women [66]

- Routine syphilis screening is not recommended for (1) men who have sex with women, (2) nonpregnant women who have sex with men, and (3) nonpregnant women who have sex with women.
- Syphilis screening may be indicated if the individual has an increased risk of acquiring syphilis (e.g., history of incarceration, transactional sex work, or other epidemiologic factors that may be associated with increased risk). In addition, syphilis screening is recommended for sexually active adults who live in counties where the rate of primary and secondary syphilis among women 15–44 years of age is greater than 4.6 per 100,000 persons.

Men Who Have Sex with Men [66,68]

- For sexually active MSM, perform syphilis screening at least annually.
- More frequent screening (every 3 to 6 months) is recommended for MSM who have an ongoing increased risk for acquiring syphilis (e.g., multiple partners, anonymous partners, and concurrent partners).

Pregnant Women [66,69]

- Syphilis serologic testing should be performed for all pregnant women at their first prenatal visit.
- Syphilis retesting should occur at 28 weeks of gestation and at delivery for women who live in a community with a high syphilis rate and for women considered to have a high risk of acquiring syphilis during pregnancy (e.g., sex with multiple partners, sex in conjunction with drug use, transactional sex work, late entry to prenatal care, methamphetamine or heroin use, incarceration of the woman or her partner, and unstable housing or homelessness).
- Any woman who delivers a stillborn infant after 20 weeks of gestation should have syphilis serologic testing.
- Screening for syphilis should occur during each pregnancy.
- In the United States, the requirements for syphilis screening in pregnancy vary by state, and clinicians should review their state’s legal requirements for syphilis screening in pregnancy.

Persons with HIV [66]

- Sexually active persons with HIV should have syphilis serologic screening at their first visit for HIV care and then at least annually thereafter.
- Persons with HIV who have a higher syphilis risk should have more frequent screening (every 3 to 6 months).

Persons Receiving HIV Preexposure Prophylaxis (HIV PrEP)

- Persons receiving HIV preexposure prophylaxis (HIV PrEP) should undergo routine syphilis serologic screening at baseline. The frequency of syphilis serologic screening for persons while they are receiving HIV PrEP varies as follows:
    - Every 3 months for MSM who are taking oral HIV PrEP (tenofovir DF-emtricitabine or tenofovir

alafenamide-emtricitabine)
    - Every 4 months for MSM who are receiving long-acting injectable cabotegravir
    - Every 6 months for men who have sex with women and women who have sex with men (with any HIV PrEP)

Persons Receiving Doxycycline Postexposure Prophylaxis (Doxy PEP) [67]

- Persons starting on doxycycline postexposure prophylaxis (doxy PEP) should undergo routine syphilis serologic screening at baseline.
- The frequency of syphilis serologic screening for persons while they are taking doxy PEP should be every 3 to 6 months.

Correctional Facilities [70]

- Routine opt-out screening for syphilis in correctional facilities should be performed based on the local area and institutional prevalence of early (primary, secondary, and early latent) infectious syphilis. Correctional facilities should stay apprised of syphilis prevalence as it changes over time.

Treatment

General Considerations

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis.[28] The preparation(s) of penicillin used (e.g., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and treatment duration depend on the stage and clinical manifestations of the disease. Benzathine penicillin G is slowly released from the intramuscular site due to extremely low solubility and is hydrolyzed to penicillin G; the combination of slow absorption and hydrolysis results in prolonged low serum levels of penicillin with this preparation. Procaine penicillin is no longer available for use in the United States.[71]

Treatment of Primary and Secondary Syphilis in Adults

Parenteral penicillin G is effective in resolving clinical symptoms associated with primary and secondary syphilis and prevents late sequelae in those who receive appropriate treatment. The recommended regimen for adults with primary and secondary syphilis is benzathine penicillin G, given as 2.4 million units once as a single intramuscular dose.[28]

Table 2. 2021 STI Treatment Guidelines: Syphilis
Treatment of Primary and Secondary Syphilis Among Adults*

*Recommendations for treating syphilis among persons with HIV infection and pregnant women are not addressed in this table.

Recommended Regimen
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy when used to treat primary and secondary syphilis, regardless of HIV status.

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

Treatment of Primary or Secondary Syphilis with Penicillin Allergy

For persons who report a penicillin allergy, it is important to determine the severity of the reaction, if the reaction was consistent with an IgE-mediated reaction, and whether the reaction occurred within the prior 10 years. Among all persons who self-reported a history of an allergic reaction to penicillin or another beta-lactam antibiotic, only 7.1% had a positive objective test that confirmed the penicillin allergy.[72] In addition, approximately 80% of persons with a true IgE-mediated allergic reaction to penicillin will lose sensitivity to penicillin after 10 years.[73] The optimal treatment of primary and secondary syphilis in persons with a true documented allergy to penicillin is unknown due to limited available data. The following summarizes alternative regimens to consider for persons allergic to penicillin; individuals receiving an alternative regimen

should have close follow-up after treatment.[28]

- **Doxycycline and Tetracycline**: Oral regimens of doxycycline (100 mg twice daily for 14 days) or tetracycline (500 mg four times daily for 14 days) can be an effective alternative for penicillin-allergic persons (except pregnant women) who have primary or secondary syphilis.[74,75] Doxycycline is preferable to tetracycline because of its less frequent dosing and fewer gastrointestinal side effects.
- **Ceftriaxone**: Intramuscular or intravenous ceftriaxone (1 gram daily for 10 days) is considered an effective alternative for treating primary and secondary syphilis in penicillin-allergic persons, but the optimal dose and duration of ceftriaxone in this setting has not been well studied.[76] Note that among persons with a history of penicillin allergy, fewer than 1.0% will have an allergic reaction to a third-generation cephalosporin, such as ceftriaxone.[77]
- **Penicillin Desensitization**: Persons with a penicillin allergy for whom concern exists about adherence or follow-up should undergo penicillin desensitization and then receive treatment with benzathine penicillin G. In addition, penicillin desensitization is recommended for pregnant women diagnosed with syphilis.[Q] Treatment of Secondary Syphilis

Treatment of Latent Syphilis in Adults

The treatment of individuals with latent syphilis requires appropriate classification into early latent syphilis (acquired less than 1 year ago, as detailed above) or late latent syphilis (acquired longer than 1 year ago). The main goal of treating persons with latent syphilis is to prevent the development of late syphilis manifestations. Early latent syphilis is treated with intramuscular benzathine penicillin G 2.4 million units given as a single dose; late latent syphilis is treated with intramuscular benzathine penicillin G 7.2 million units total, which is split into three weekly doses, each with 2.4 million units.[28] Alternative therapies for the treatment of latent syphilis have not been well studied.[28]

Table 3. 2021 STI Treatment Guidelines: Syphilis
Treatment of Latent Syphilis Among Adults*

*Recommendations for treating syphilis in persons with HIV and pregnant women are not addressed in this table.

Recommended Regimen for Early Latent Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV status.

Recommended Regimen for Late Latent Syphilis
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

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

Treatment of Latent Syphilis in Persons Allergic to Penicillin

For penicillin-allergic persons (except for pregnant women) with early latent syphilis, the treatment approach and regimens should be the same as for penicillin-allergic persons with primary or secondary syphilis. For penicillin-allergic individuals (except for pregnant women) with late latent syphilis, the only acceptable treatment alternatives are a 28-day course of oral therapy with either doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily).[28] Ceftriaxone may be a reasonable option in this setting, but the optimal number of doses or schedule has not been determined, and use of ceftriaxone to treat latent syphilis should involve consultation with a specialist.[28] All persons treated with an alternative regimen should have close serologic and clinical follow-up, especially individuals with HIV. Persons for whom adherence and follow-up are a concern should ideally undergo penicillin desensitization and receive treatment with benzathine penicillin G.[28] Pregnant women with latent syphilis who are allergic to penicillin should undergo penicillin desensitization and receive appropriate treatment with penicillin.[28]

Treatment of Tertiary Syphilis in Adults

The recommended regimen for tertiary syphilis (without evidence of neurosyphilis) is benzathine penicillin G 7.2 million units total divided into three weekly intramuscular injections of 2.4 million units with each dose.[28] All persons diagnosed with tertiary syphilis should undergo a CSF examination prior to starting therapy due to the high rates of neurosyphilis that is not clinically apparent.[28] Some experts treat tertiary cardiovascular syphilis with a neurosyphilis regimen, regardless of the CSF results.[28]

Table 4. 2021 STI Treatment Guidelines: Syphilis
Treatment of Tertiary Syphilis Among Adults

Recommended Regimen for Treatment of Tertiary Syphilis with Normal CSF Examination
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin.

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

Treatment of Tertiary Syphilis in Persons Allergic to Penicillin

Persons diagnosed with tertiary syphilis who have a documented penicillin allergy should also receive syphilis treatment in consultation with an expert; for these individuals, there is inadequate data for any alternative regimens.[28] Pregnant women with tertiary syphilis who are allergic to penicillin should undergo penicillin desensitization and receive appropriate treatment with penicillin.[28]

Treatment of Neurosyphilis, Ocular Syphilis, and Otosyphilis in Adults

The recommended treatment regimen for neurosyphilis, ocular syphilis, and otosyphilis is aqueous crystalline penicillin G 18-24 million units per day, given as 3-4 million units intravenously every 4 hours (or as

continuous infusion), for a total of 10 to 14 days.[28] Some experts recommend giving additional therapy with one dose of intramuscular benzathine penicillin G 2.4 million units after completing the 10- to 14-day regimen in order to provide a total duration of therapy comparable to the treatment for late latent syphilis. Although this approach is sometimes used, data are lacking to support this enhanced treatment regimen.[28] Daily intramuscular procaine penicillin G is no longer available for use and thus is not a treatment option (instead of aqueous intravenous penicillin). There are insufficient data to support the use of systemic corticosteroids as adjunctive therapy for neurosyphilis, ocular syphilis, or otosyphilis.[28]

Table 5. 2021 STI Treatment Guidelines: Syphilis
Treatment of Neurosyphilis, Ocular Syphilis, or Otosyphilis Among Adults

Note: procaine penicillin G is no longer available for use and therefore is not included in this table.

Recommended Regimen
Aqueous crystalline penicillin G *18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days*

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

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

Treatment of Neurosyphilis in Persons Allergic to Penicillin

Limited data suggest that intramuscular or intravenous ceftriaxone 1–2 grams daily for 10 to 14 days can be used as an alternative treatment for persons with neurosyphilis who are allergic to penicillin.[28,78] Other regimens have not been adequately studied for use in persons with neurosyphilis. Pregnant women who are allergic to penicillin and are diagnosed with neurosyphilis, ocular syphilis, or otosyphilis should undergo penicillin desensitization and receive appropriate treatment with penicillin.[28][Q] Treatment of Neurosyphilis

Treatment of Syphilis in Adults with HIV

The recommended treatment of all stages of syphilis (primary, secondary, latent, or tertiary) and neurosyphilis in persons with HIV is the same as for persons without HIV.[28] Available data suggest that persons with HIV may have an increased risk of developing neurologic complications and may have higher rates of treatment failure (based on inadequate serologic response).[28,79] All persons with HIV who are diagnosed with syphilis should undergo careful neurologic, ocular, and otic symptom review and examination, and those with abnormal neurologic findings should promptly undergo lumbar puncture for CSF examination.[28] Initiation of antiretroviral therapy for HIV concurrently with syphilis treatment may improve clinical response to syphilis treatment.[80]

Table 6. 2021 STI Treatment Guidelines: Syphilis
Treatment of Syphilis Among Persons with HIV

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

Recommended Regimen for Treatment of Primary and Secondary Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis among persons with HIV do not result in enhanced efficacy.

Recommended Regimen for Treatment of Early Latent Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*

Recommended Regimen for Treatment of Late Latent or Latent Syphilis of Unknown Duration
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

Recommended Regimen for Treatment of Neurosyphilis, Ocular Syphilis, and Otic Syphilis
Aqueous crystalline penicillin G *18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days*
Note: The duration of the recommended regimen for neurosyphilis is shorter than the duration of the regimen used for treatment of latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of neurosyphilis treatment to provide a total duration of therapy comparable to treatment of latent syphilis.

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

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Delays in Treatment Doses

For persons scheduled to receive a weekly 3-dose benzathine penicillin G treatment regimen, unplanned delays can occur between the scheduled weekly doses. When these delays occur, the optimal management is not clear. Although the pharmacokinetic profile of benzathine penicillin G suggests an interval of 7 to 9 days between doses is optimal and preferred, clinical experience suggests that an interval of 10 to 14 days between doses for the treatment of late latent syphilis (or latent syphilis with unknown duration) might be acceptable.[23] For persons undergoing treatment (except pregnant women), an interval greater than 10 to 14 days warrants restarting therapy. For pregnant women, if the interval between penicillin doses exceeds 9 days, the 3-dose benzathine penicillin G treatment regimen should start over.[28,81]

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is a self-limited reaction associated with the initiation of syphilis treatment. This reaction represents a systemic inflammatory response following the antimicrobial treatment of *T. pallidum*—it is not an allergic reaction to penicillin. The Jarisch-Herxheimer reaction most often involves persons treated for early syphilis, particularly secondary syphilis, presumably because of the higher bacterial burden during the early stages.[28] When this reaction occurs, it typically begins within several hours of the initiation of antimicrobial treatment and nearly always within 24 hours. The Jarisch-Herxheimer reaction is characterized by fever, malaise, nausea, vomiting, and, less frequently, chills, hypotension, or an exacerbation of a secondary syphilis rash.[82] This reaction can be mistaken for an allergic reaction to penicillin. Accordingly, it is important to carefully evaluate any reaction that begins within 24 hours of treatment for syphilis and carefully sort out the likelihood of a Jarisch-Herxheimer reaction versus an allergic reaction to penicillin. The management of Jarisch-Herxheimer is supportive care, primarily with fluids and antipyretics; typically, the reaction resolves spontaneously within 24 hours.[17]

Post-Treatment Follow Up

The follow-up of persons with syphilis after treatment is extremely important to document response to therapy and to reevaluate for reinfection. The post-treatment laboratory monitoring should use nontreponemal tests (RPR or VDRL), and the same type of test (RPR or VDRL) should consistently be used for comparison of quantitative nontreponemal titers.[43] Typically, RPR and VDRL titers are not equivalent, with RPR titers slightly higher than VDRL titers. Changes in nontreponemal titers are described as a quantitative "fold" decrease or increase, based on the comparison of the most recent nontreponemal titer and prior nontreponemal titer (Figure 11).

Post-Treatment Follow-Up Testing Schedule

The following are general recommendations for follow-up after syphilis treatment.[28]

Primary and Secondary Syphilis

- Persons without HIV who are treated for primary or secondary syphilis should be reexamined clinically and serologically at 6 months and 12 months following treatment. Clinicians should allow for a full 12 months of follow-up to determine if the titers have declined appropriately (at least a 4-fold decrease) in persons treated for primary or secondary syphilis.
- Individuals with HIV should have post-treatment follow-up for primary or secondary syphilis at 3, 6, 9, 12, and 24 months; since treatment response may be delayed in persons with HIV, a full 24 months of follow-up should be allowed for the response.

Latent Syphilis

- Persons without HIV who are treated for latent syphilis should have clinical and nontreponemal serologic follow-up at 6, 12, and 24 months.
- For persons with HIV, this follow-up should occur at 6, 12, 18, and 24 months.
- Clinicians should allow for a full 24 months of follow-up to determine if the titers have declined appropriately (at least a 4-fold decrease) in persons treated for latent syphilis, with or without HIV.

Neurosyphilis, Ocular Syphilis, and Otosyphilis

- Available data suggest that for immunocompetent persons without HIV (and persons with HIV on antiretroviral therapy), a normalization of the serum RPR or VDRL titers following syphilis treatment correlates with normalization of abnormal CSF parameters.[83,84] Accordingly, persons treated for neurosyphilis who have good clinical and nontreponemal serologic responses (RPR or VDRL) do not require follow-up lumbar puncture and CSF evaluation. The serologic nontreponemal titer follow-up for persons treated for neurosyphilis, ocular syphilis, and otosyphilis should be based on their stage of syphilis and their HIV status. For example, if a person without HIV is concomitantly diagnosed with secondary syphilis and neurosyphilis, their follow-up should be serologic testing at 6 and 12 months following treatment, allowing for a full 12 months of follow-up to determine if the titers have declined appropriately.

Follow-Up Management

A key reason for close follow-up of persons treated for syphilis is to monitor signs, symptoms, or serologic changes in nontreponemal titers that indicate possible treatment failure or reinfection. In general, the goal is to achieve a 4-fold or greater decline in nontreponemal titer, and this is often referred to as having an "adequate serologic response" or "serologic cure." In contrast, the failure to achieve a 4-fold or greater decline in the nontreponemal titer within an appropriate timeframe after treatment is termed "inadequate serologic response" or "lack of serologic response" or "serologic nonresponse."[28,85] Several factors have

been identified with a lack of 4-fold decline in nontreponemal titers, including a lower pretreatment titer (e.g., less than 1:8), older age, and later stage of syphilis. A slower decline in titers has been associated with prior history of syphilis treatment and HIV infection.[85,86] The term “serofast” has also been used to describe any persistent nontreponemal titer after treatment, including inadequate serologic response and persistently positive nontreponemal titers despite an appropriate 4-fold decline in titers.[87,88] The following summarizes the recommended evaluation and management of several post-treatment scenarios.[28]

Probable Reinfection or Treatment Failure

Reinfection or treatment failure is likely if any of the following occur: (1) an individual has syphilis-related signs or symptoms that persist or recur, (2) the person experiences new syphilis signs or symptoms attributable to primary or secondary syphilis, or (3) repeated serologic testing shows a 4-fold (or greater) increase in nontreponemal titer that is sustained (persists for longer than 2 weeks). In any of these situations, HIV testing should be performed, unless the person is known to have HIV. Evaluation for neurosyphilis with lumbar puncture and CSF evaluation is recommended if new neurologic manifestations are present or there are no recent sexual exposures (in the prior 6 months in persons treated for primary or secondary syphilis and the prior 12 months for persons treated for latent and other stages of syphilis); treatment is then guided based on the CSF evaluation. A sexually active person who does not have new neurologic manifestations, or a person in whom the CSF evaluation has ruled out neurosyphilis, retreatment is recommended with one dose of intramuscular benzathine penicillin G 2.4 million units for those previously diagnosed with primary or secondary syphilis. All others should receive retreatment with three doses of intramuscular benzathine penicillin G 2.4 million units given weekly for 3 weeks.

Inadequate Serologic Response

For persons who fail to achieve at least a post-treatment 4-fold decline in nontreponemal titers within the recommended timeframe (12 months for primary or secondary syphilis, 24 months for latent syphilis, and 24 months for any stage of syphilis in persons with HIV), the optimal management is unknown. The evaluation of persons with inadequate serologic response should include, at a minimum, HIV testing, neurologic examination, and a yearly clinical follow-up that includes repeated syphilis serologic studies. Syphilis retreatment is recommended when follow-up cannot be ensured, or the person had an initial high titer (greater than 1:32) that did not decrease at least 4-fold in the expected timeframe. The recommended retreatment regimen consists of weekly intramuscular injections of benzathine penicillin G 2.4 million units for 3 weeks. In this setting, however, several observational studies showed failure of nontreponemal titers to decline after retreatment with additional antibiotics.[87,89] If, at any point, the person has neurologic signs or symptoms, then analysis of CSF should be performed with treatment guided by the CSF results; some experts would consider performing CSF analysis if a fourfold decline was not achieved in the 12-month post-treatment period, even without neurologic signs or symptoms.

Lack of Seroreversion

Some individuals will achieve a 4-fold or greater decline in the nontreponemal titer after treatment but have persistently reactive nontreponemal titers; this situation is usually referred to as lack of seroreversion.[85,90] There is increasing evidence that providing additional antibiotic treatment for these individuals does not change outcomes and does not significantly change nontreponemal titers.[88,89] Therefore, in the absence of clinical evidence for reinfection or new neurologic manifestations, most experts would not recommend retreatment in this setting.

Management of Sex Partners

Evaluation and Treatment of Sex Partners

In general, the transmission of *T. pallidum* between sex partners only occurs when the person with syphilis has mucocutaneous lesions. In general, all persons who have sexual contact with a person diagnosed with primary, secondary, or early latent syphilis infection should undergo evaluation, testing, and treatment for syphilis, as outlined below.[28]

- For persons diagnosed with primary, secondary, or early latent syphilis, all sex partners in the 90 days preceding the syphilis diagnosis should be notified, undergo clinical evaluation, have syphilis serologic studies obtained, and receive presumptive treatment for early syphilis, even if serologic test results are negative.
- Persons who had sexual contact with an individual who was diagnosed with primary, secondary, or early latent syphilis, but the contact occurred more than 90 days before the syphilis diagnosis, should be notified and undergo clinical evaluation and syphilis serologic testing. The sex partner should be treated presumptively for early syphilis if serologic test results are not immediately available and follow-up is uncertain. Alternatively, if follow-up is reliable, treatment can be based on syphilis serologic test results; for persons with negative serologic tests, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis.
- In some areas or populations with high rates of syphilis, health departments recommend notification and presumptive treatment of sex partners of persons with late latent syphilis who have high nontreponemal serologic test titers (i.e., greater than 1:32) because high titers might be indicative of early syphilis. These partners should be managed as if the index case had early syphilis.
- Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated based on these findings.
- Certain sex partners of persons with syphilis are considered at risk of infection and should be confidentially notified of the exposure and the need for evaluation. These include partners who have had sexual contact (1) within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, (2) within 6 months plus the duration of symptoms for those with secondary syphilis, and (3) within 1 year for persons with early latent syphilis. For example, if a person had symptoms of secondary syphilis for 1 month, then any sex partner in the prior 4 months should be considered at risk for syphilis and undergo evaluation and treatment.

Expedited Partner Therapy

Expedited partner therapy is not recommended for the sexual contacts of persons diagnosed with syphilis.

Counseling and Education

The following summarizes key counseling messages for persons diagnosed with syphilis.

- **Resuming Sexual Activity**: Persons treated for syphilis infection should be informed that they can transmit syphilis to others during the primary and secondary stages of syphilis (when mucosal lesions or rashes are present). They should abstain from sexual activity until the following criteria are met: (1) at least 7 days have elapsed since completing syphilis treatment, (2) all mucosal and skin lesions have resolved, and (3) sex partners have been treated for syphilis.
- **Partner Notification**: It is extremely important that persons treated for syphilis understand the importance of partner notification (for all sex partners in the prior 90 days). Partner notification with evaluation and treatment can markedly reduce the spread of STIs in the community, and it also reduces the likelihood of reinfection for the person diagnosed with syphilis.
- **Follow-Up Testing**: It is important that all persons treated for syphilis have follow-up visits for clinical evaluation and serial nontreponemal serologic testing to evaluate response to syphilis treatment.
- **HIV Preexposure Prophylaxis**: Men who have sex with men who are diagnosed with syphilis have a substantial risk of acquiring HIV and, therefore, should be offered HIV preexposure prophylaxis (PrEP). All other persons diagnosed with syphilis should be evaluated for potential HIV preexposure prophylaxis on a case-by-case basis.
- **STI Prevention**: At the time a person is receiving treatment for an STI, it is appropriate to provide counseling messages on how to prevent STIs in the future (e.g., limiting the number of sex partners and consistently using condoms).

Prevention

Doxycycline PostExposure Prophylaxis for Prevention of STIs

Doxycycline, administered as a 200-mg single dose within 72 hours after a condomless sexual encounter, can help prevent bacterial STIs, including chlamydia, syphilis, and gonorrhea. The use of doxycycline postexposure prophylaxis (doxy PEP) has been shown to be effective for men who have sex with men in several randomized trials.[91,92,93] One clinical trial using doxy PEP for women in Africa did not show benefit in reducing STIs.[94] In 2024, the CDC published *Clinical Guidelines on the Use of Doxycycline Post-exposure Prophylaxis for Bacterial STI Prevention*.[67] These guidelines do not recommend doxy PEP for women. The following will focus on the impact of doxy PEP on preventing syphilis.

Doxycycline Postexposure Prophylaxis for Prevention of Syphilis

Doxy PEP is effective at preventing syphilis in MSM. In the DoxyPEP randomized trial conducted in San Francisco and Seattle, the quarterly incidence of new syphilis infections was statistically lower (0.4%) in the doxy PEP arm than in the standard of care arm (2.7%) and trended toward lower with use of doxy PEP in persons with HIV (0.7% vs 2.3%).[93] In the ANRS DOXYVAC randomized trial, among MSM taking HIV PrEP, the incidence (per 100 person-years) of the first episode of syphilis was 2.9 in the doxy PEP arm compared to 14.5 in the standard of care arm.[92] Similarly, in the IPERGAY-DoxyPEP study, the use of doxy PEP among 232 MSM taking HIV PrEP led to a 73% relative risk reduction in the occurrence of syphilis.[91]

Summary Points

- In the United States, reported cases of syphilis, including congenital syphilis, have significantly increased overall in the past decade.
- Syphilis is a systemic infection caused by *Treponema pallidum*, and in the absence of treatment, this disease can progress in stages. Neurosyphilis, ocular syphilis, and otosyphilis can occur during any stage of infection.
- Untreated syphilis in pregnancy can lead to devastating consequences, including stillbirth, neonatal death, and congenital syphilis.
- The laboratory diagnosis of syphilis is challenging and requires using a combination of clinical criteria and laboratory tests (both treponemal and nontreponemal tests) to differentiate active infection, prior infection, and absence of infection.
- The serologic diagnosis of syphilis employs two major algorithms: (1) the traditional screening method that uses a nontreponemal assay (RPR or VDRL) as the initial test, or (2) a reverse sequence screening method that uses a treponemal antibody test (EIA or CIA) as the initial test.
- Screening for syphilis is recommended in all pregnant women, men who have sex with men, persons with HIV, and other groups at increased risk for acquisition of syphilis.
- Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis and is effective in resolving clinical symptoms associated with primary and secondary syphilis, as well as preventing late sequelae. The dosing of penicillin depends on the stage of disease; neurologic, ocular, and otosyphilis require more intensive therapy.
- For a person diagnosed with primary, secondary, or early latent syphilis, all of their sex partners within the prior 90 days should undergo evaluation and treatment of syphilis; if no sexual contacts occurred in the 90 days prior to the diagnosis, then the most recent sex partner should have evaluation and presumptive treatment.
- All persons treated for syphilis should have follow-up monitoring with nontreponemal (RPR or VDRL) testing to evaluate response to treatment.
- The use of doxy PEP in MSM is a new prevention tool that reduces the risk of syphilis by approximately 70%.

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[PubMed Abstract] -

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[PubMed Abstract] -

Figures

Figure 1 Natural History and Clinical Staging of Syphilis

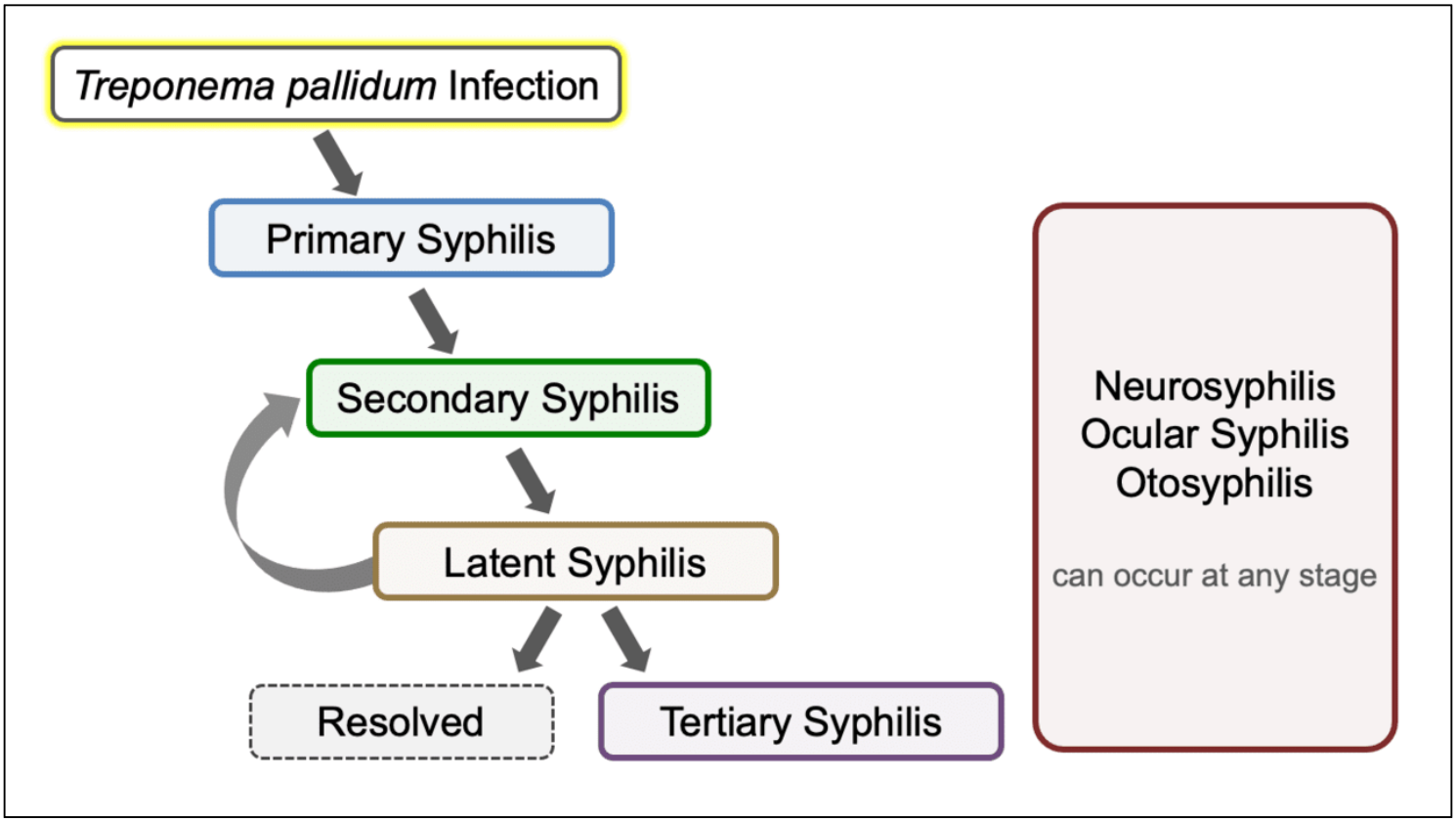

Figure 2 Syphilis Epidemiology in the United States

Source: Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023. Atlanta: U.S. Department of Health and Human Services; November 2024.

This is a dynamic visualization. Please visit our website to experience this dynamic content.

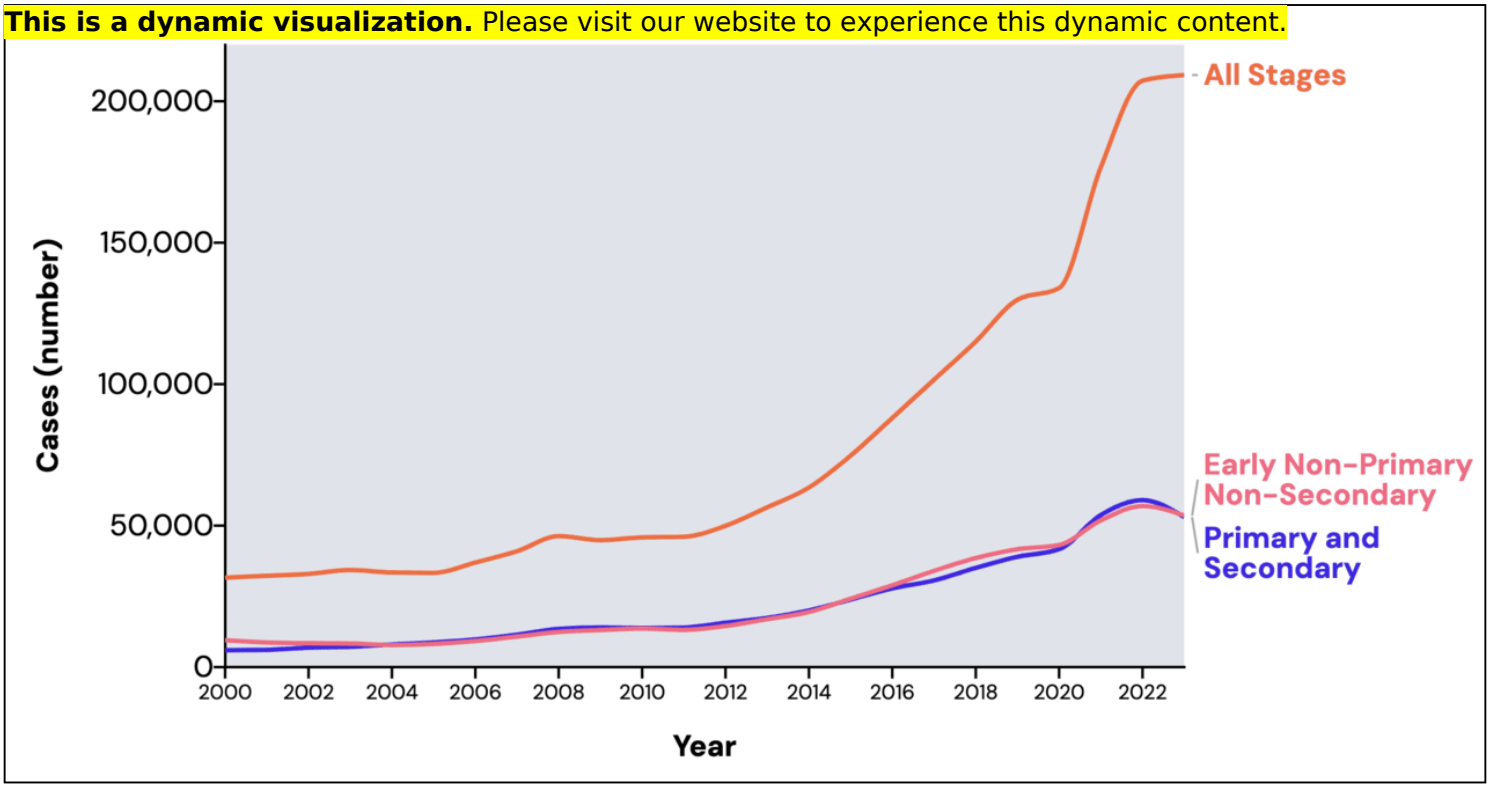

Figure 3 (Image Series) - *Treponema pallidum* (Image Series) - Figure 3 (Image Series) - *Treponema pallidum*
Image 3A: *Treponema pallidum*—Electron Micrograph

This electron micrograph shows the 'corkscrew' shape of *Treponema pallidum* growing in cultures of cottontail rabbit epithelium cells.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Dr. David Cox).

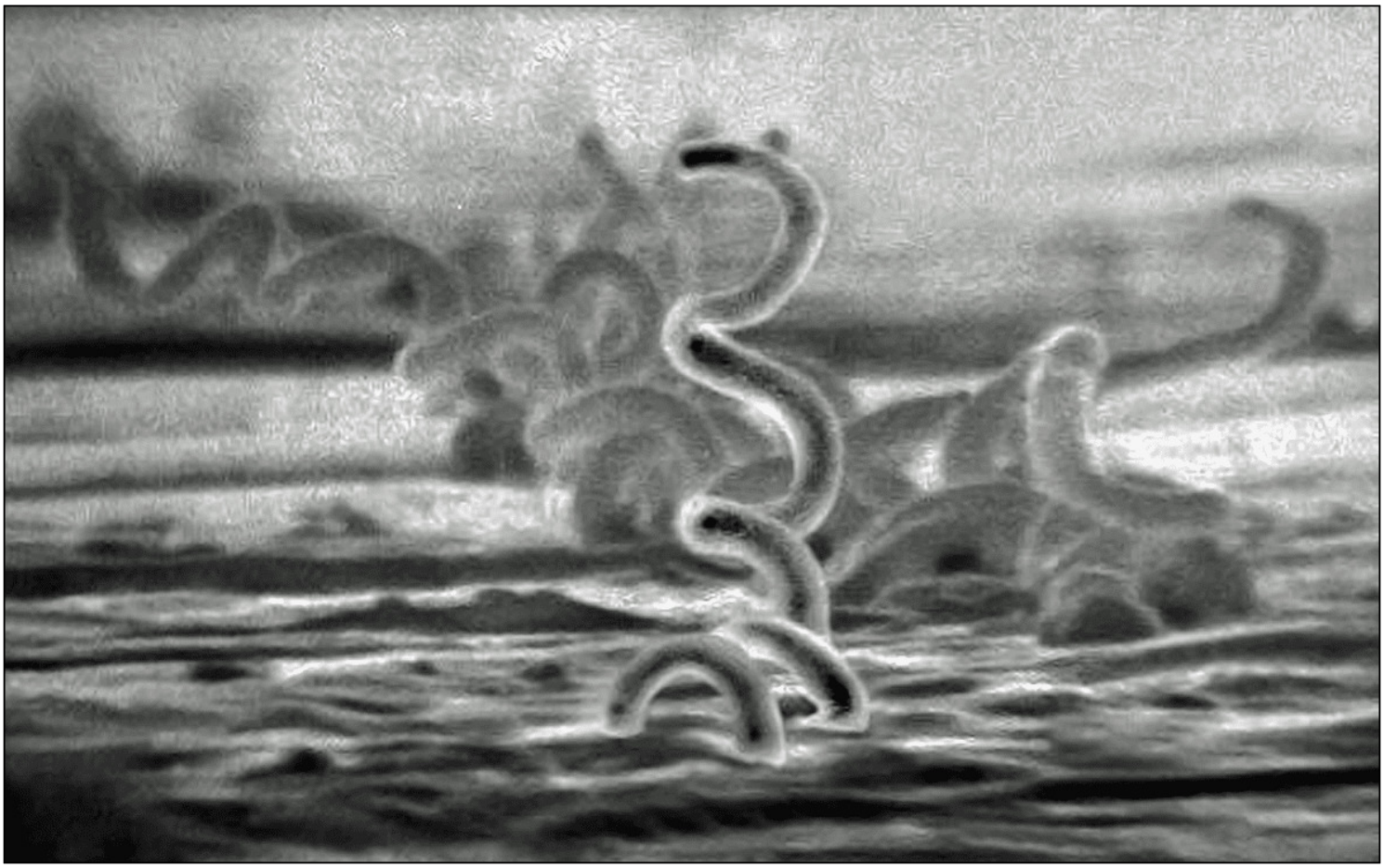

Figure 3 (Image Series) - *Treponema pallidum*
Image 3B: *Treponema pallidum*—Photomicrograph

This photomicrograph shows an isolated *Treponema pallidum* spirochete bacterium approximately 6 to 20 micrometers in length and 0.1 to 0.18 micrometers in width.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Susan Lindsley, 1972).

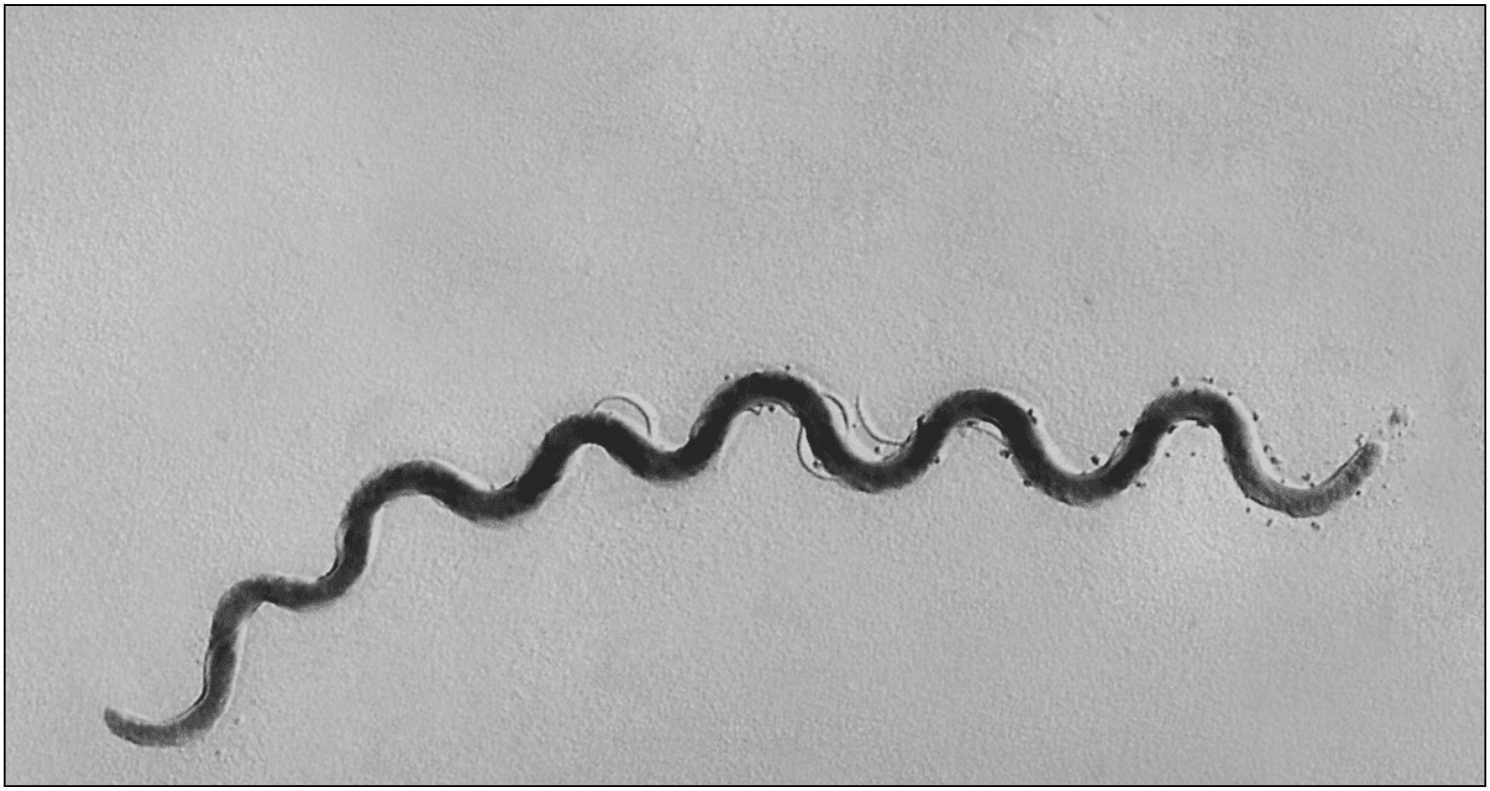

Figure 4 (Image Series) - Primary Syphilis (Image Series) - Figure 4 (Image Series) - Primary Syphilis
Image 4A: Primary Syphilis—Oral Chancre

This man with primary syphilis developed an oral chancre on the tongue

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

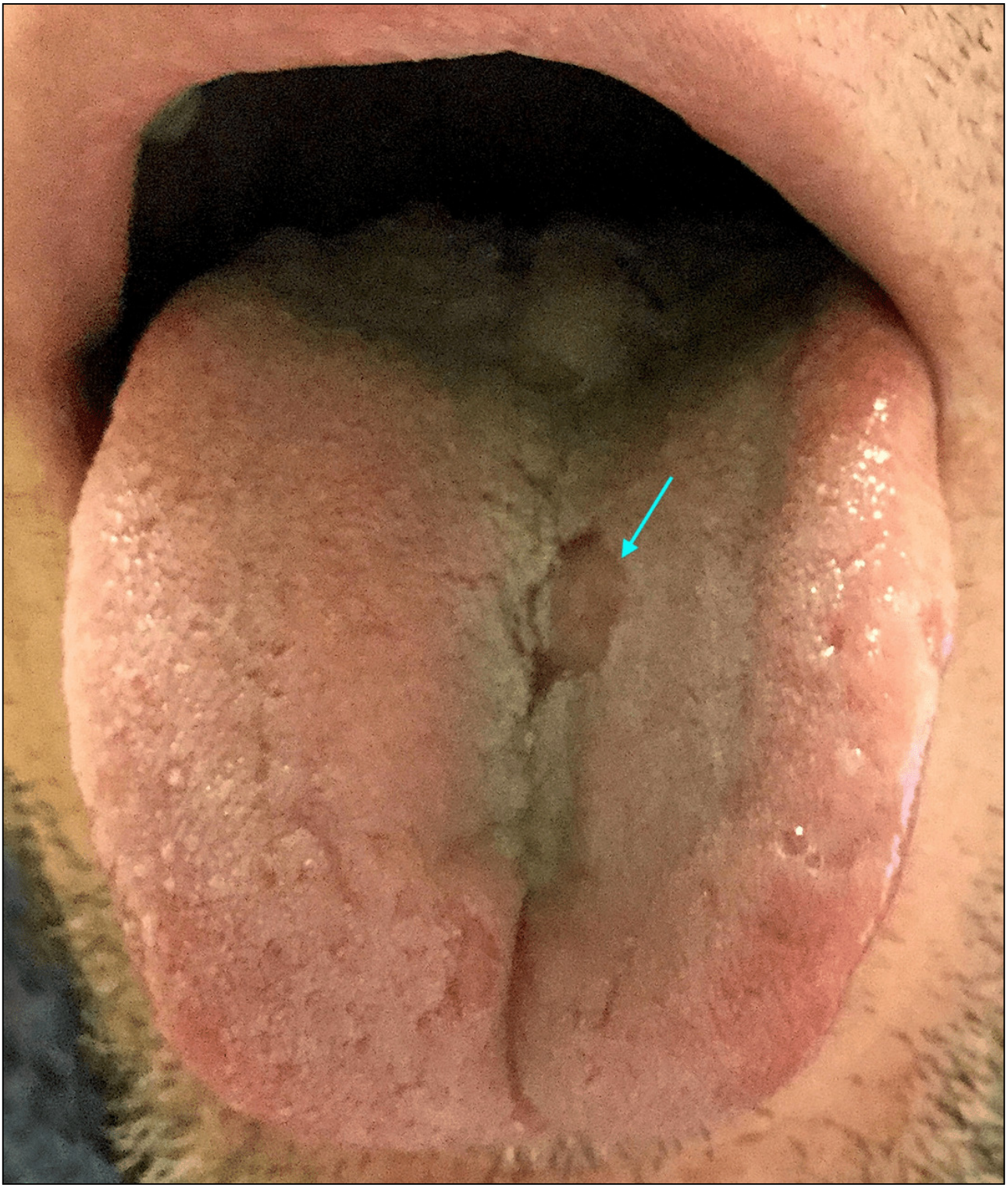

Figure 4 (Image Series) - Primary Syphilis
Image 4B: Primary Syphilis—Penile Chancre

This man with primary syphilis had a large, firm, non-painful, ulcerated lesion on the penis accompanied by right-sided inguinal adenopathy.

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

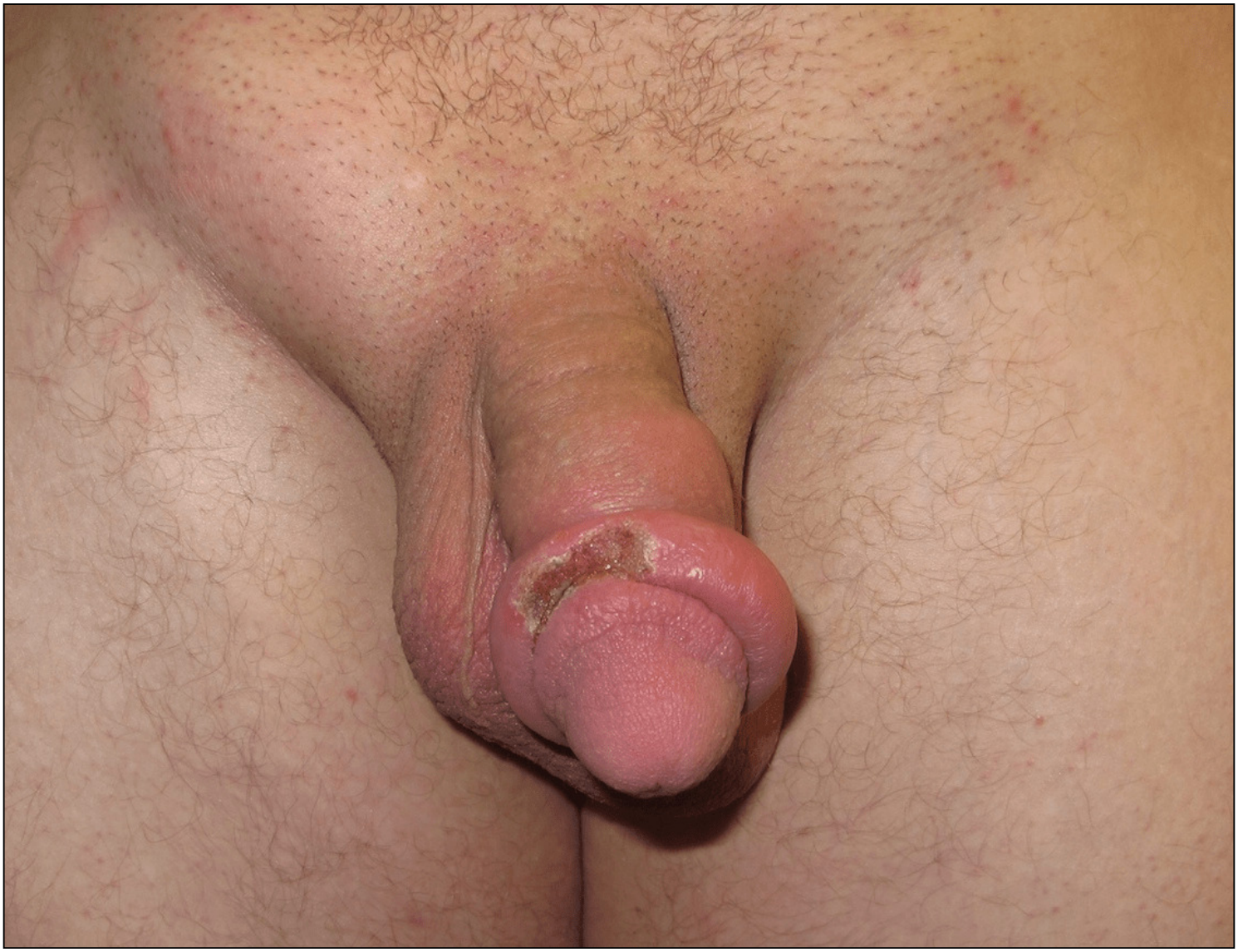

Figure 5 (Image Series) - Secondary Syphilis—Rash (Image Series) - Figure 5 (Image Series) - Secondary Syphilis—Rash
Image 5A: Diffuse Rash on Chest

This patient with secondary syphilis developed a diffuse erythematous macular rash prominent on the chest, back, palms, and soles.

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

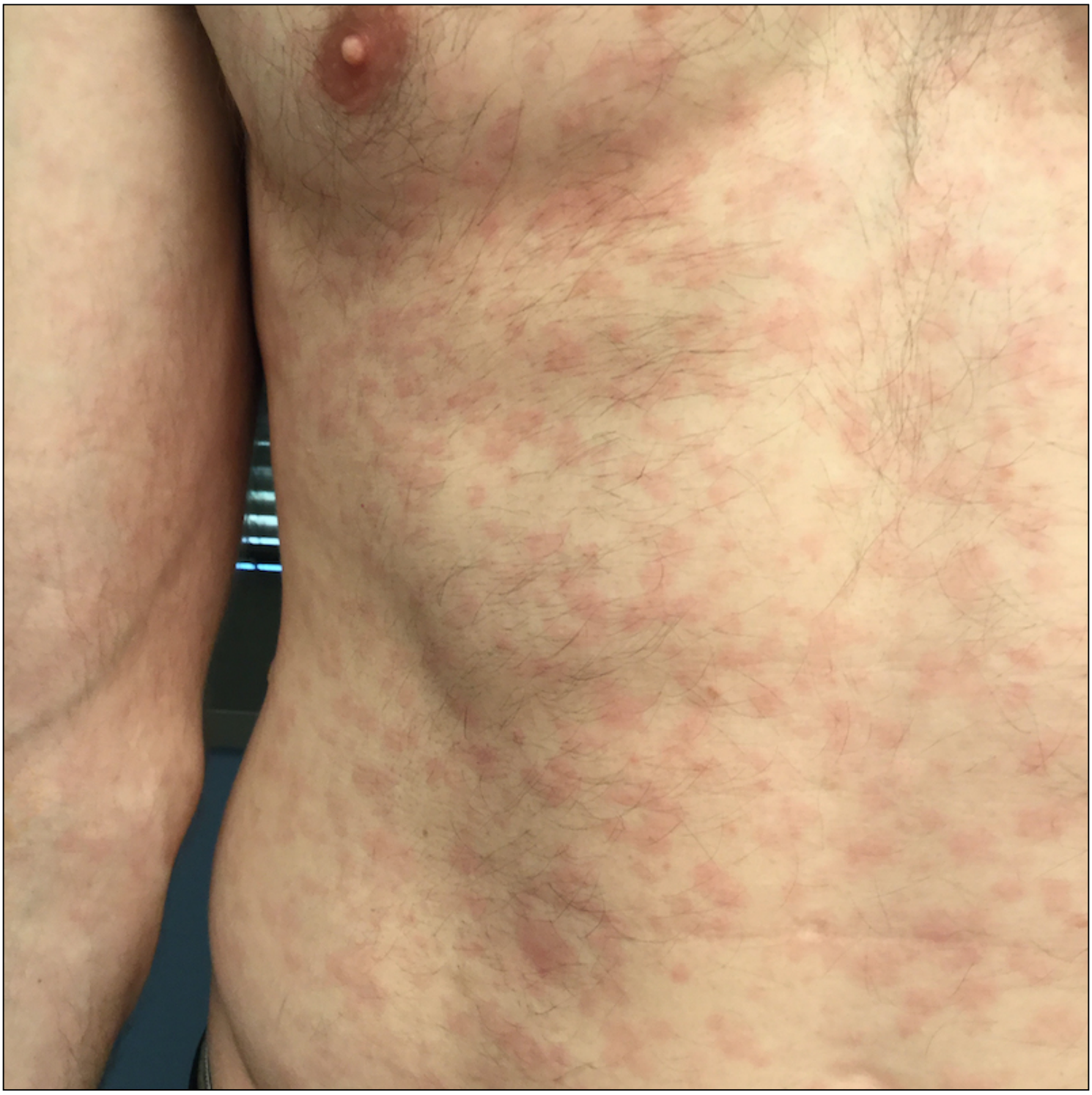

Figure 5 (Image Series) - Secondary Syphilis—Rash
Image 5B: Maculopapular Rash on Feet

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

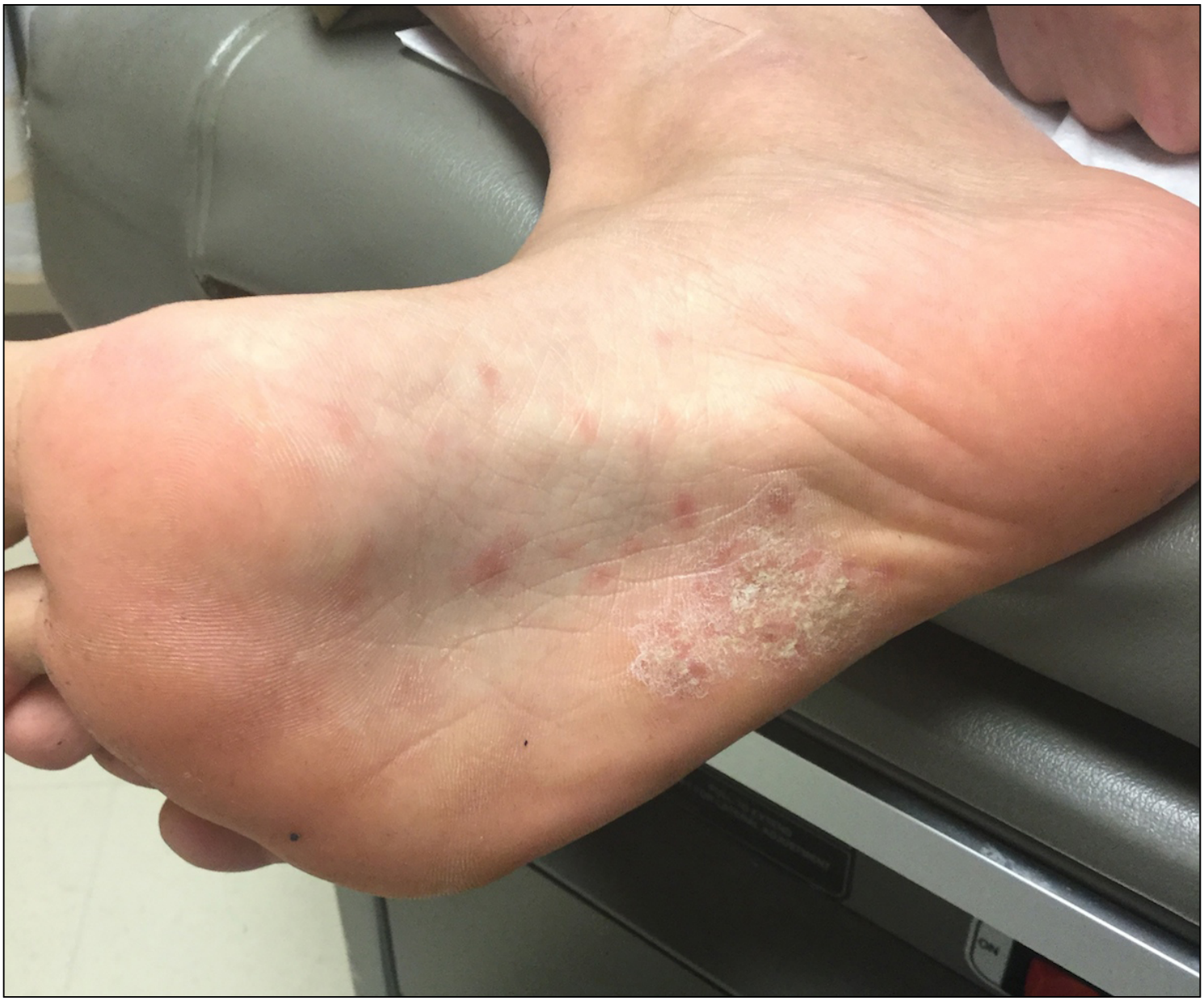

Figure 5 (Image Series) - Secondary Syphilis—Rash
Image 5C: Secondary Syphilis—Oral Lesions

This patient with secondary syphilis had multiple shallow ulcerations on the tongue (black arrows).

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

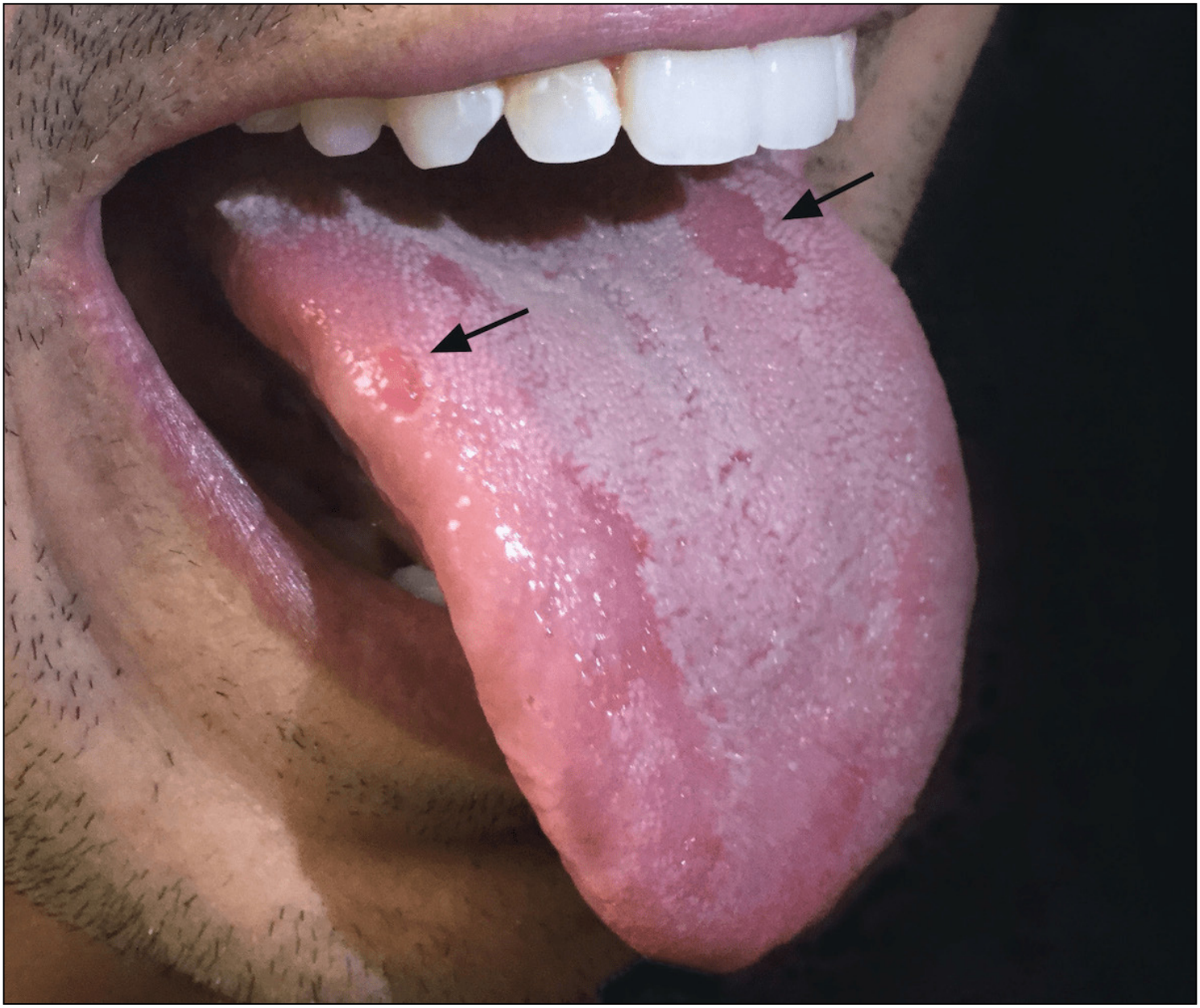

Figure 5 (Image Series) - Secondary Syphilis—Rash
Image 5D: Secondary Syphilis—Condylomata lata

This patient with secondary syphilis developed multiple vulvar and intertriginous condylomata lata lesions; these lesions typically appear as moist, gray, raised papules, often resembling warts (condyloma acuminata).

Photograph credit: Centers for Disease Control and Prevention Public Health Image Library (CDC/J.Pledger, 1976).

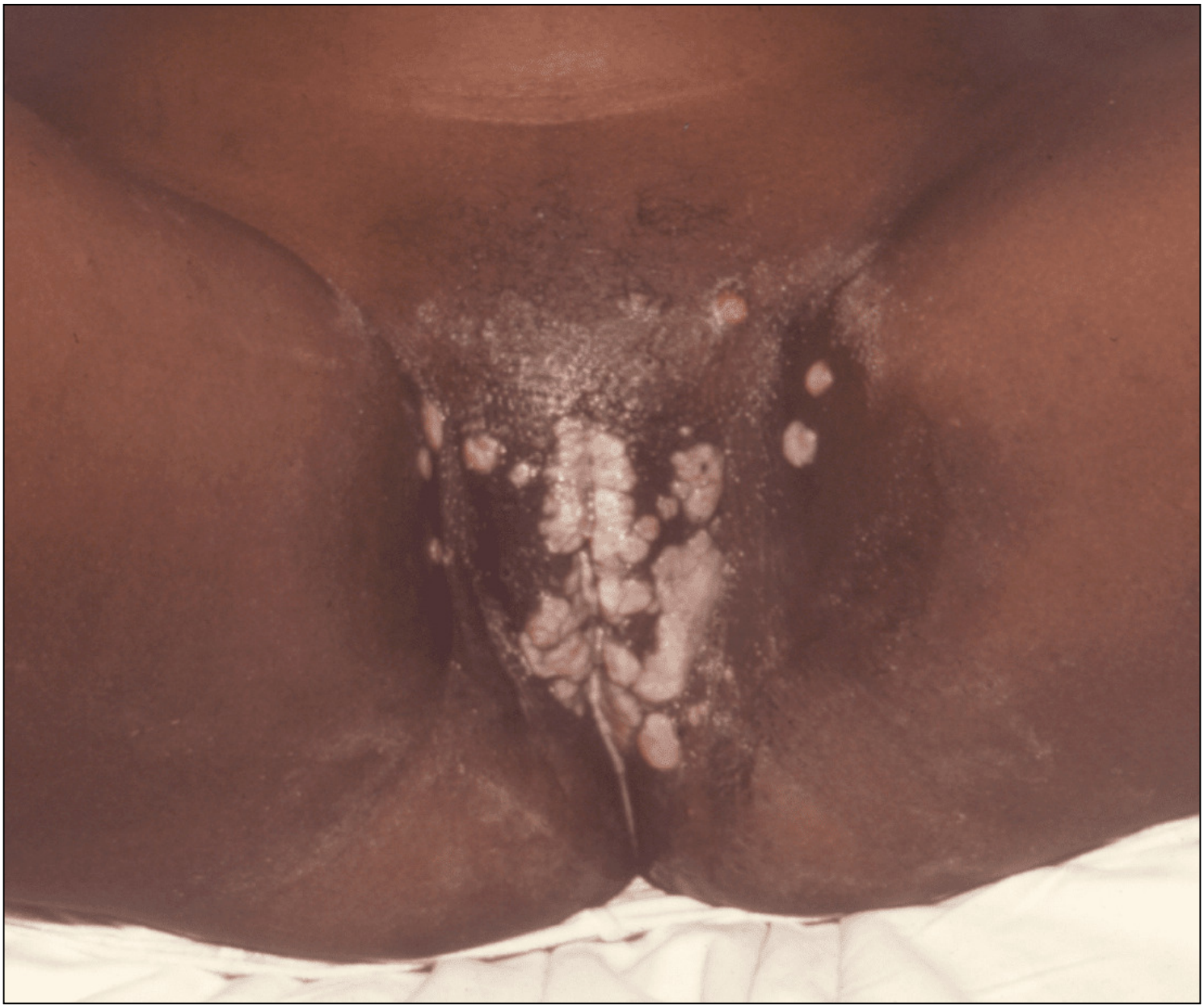

Figure 6 Normal Eye Anatomy

The uvea includes three structures: iris, ciliary body, and choroid

Illustration by David Ehlert, Cognition Studio, Inc.

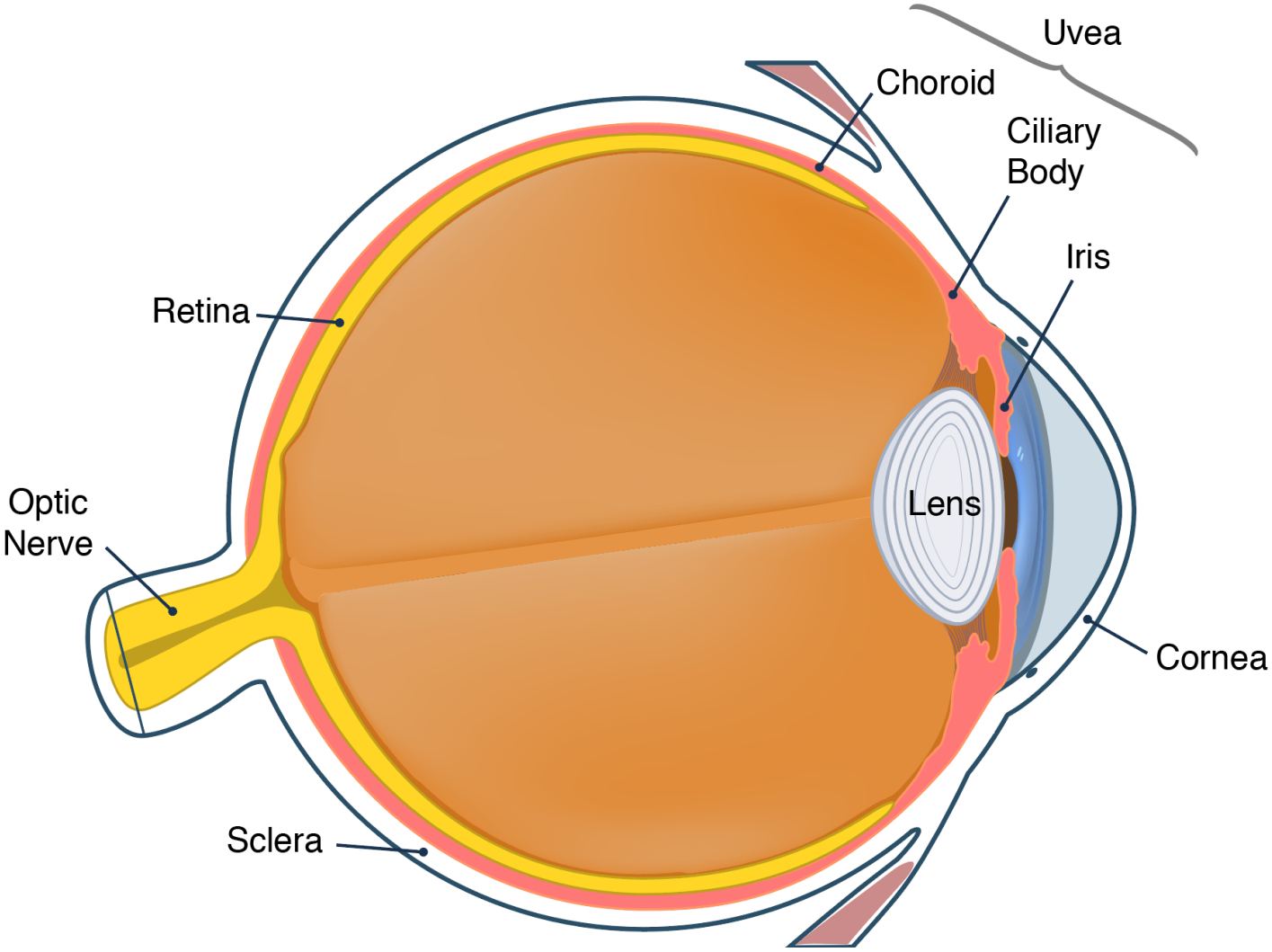

Figure 7 *Treponema pallidum*—Dark-Field Microscopy

This photomicrograph shows the typical 'corkscrew' appearance of several *Treponema pallidum* spirochetes with the dark-field microscopy technique.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Renelle Woodall, 1969).

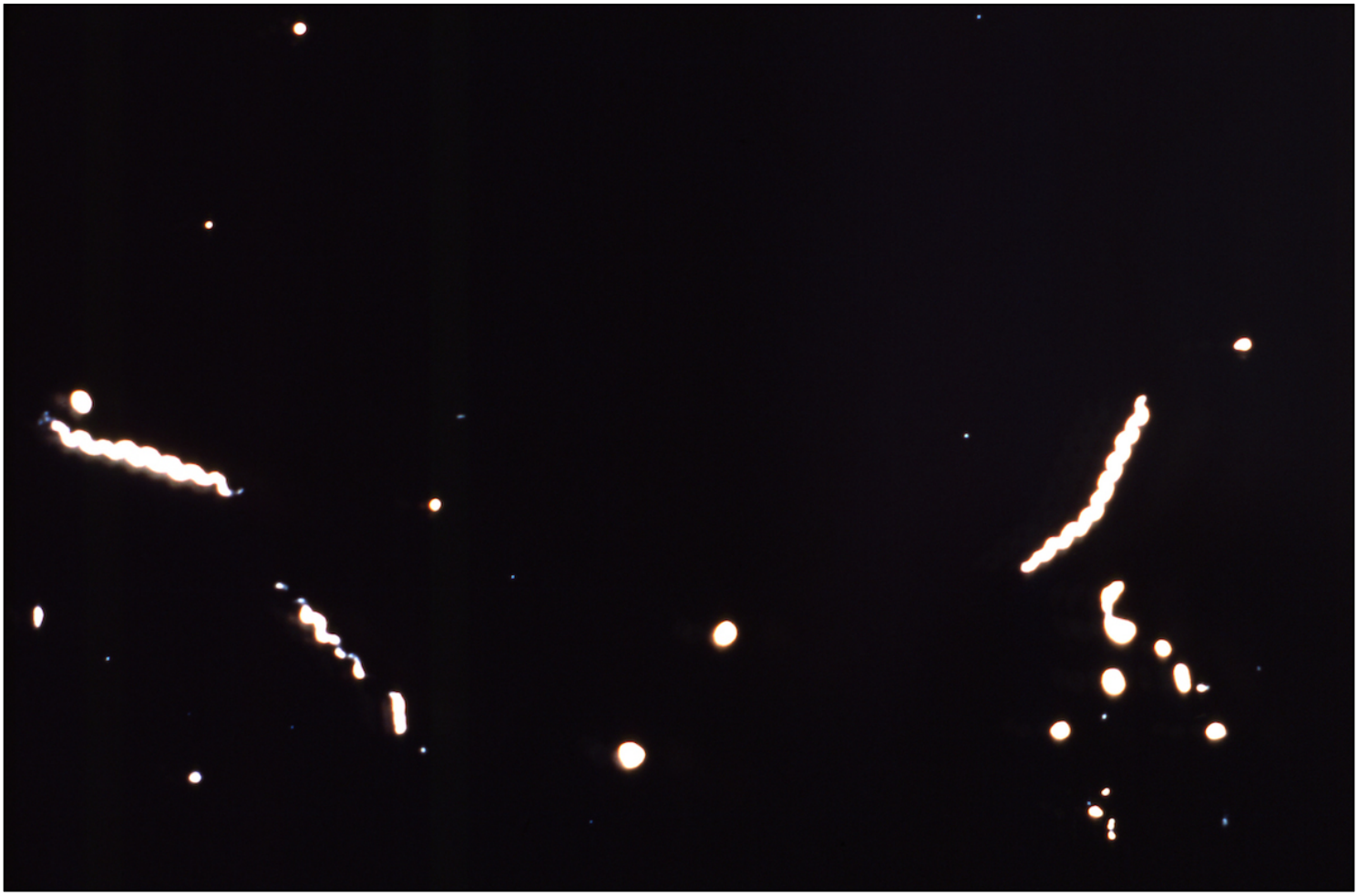

Figure 8 *Treponema pallidum* Indirect Fluorescent Antibody (IFA) Serologic Test

The fluorescent treponemal antibody absorption (FTA-ABS) test uses indirect fluorescent antibody technique in serum samples. This image shows abundant *Treponema pallidum* spirochetes with the use of a sample treated with Fluorescent Treponemal Antibody (FTA) antigen. The specimen shown here is enhanced by ultraviolet (UV) illumination.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Russell, 1967).

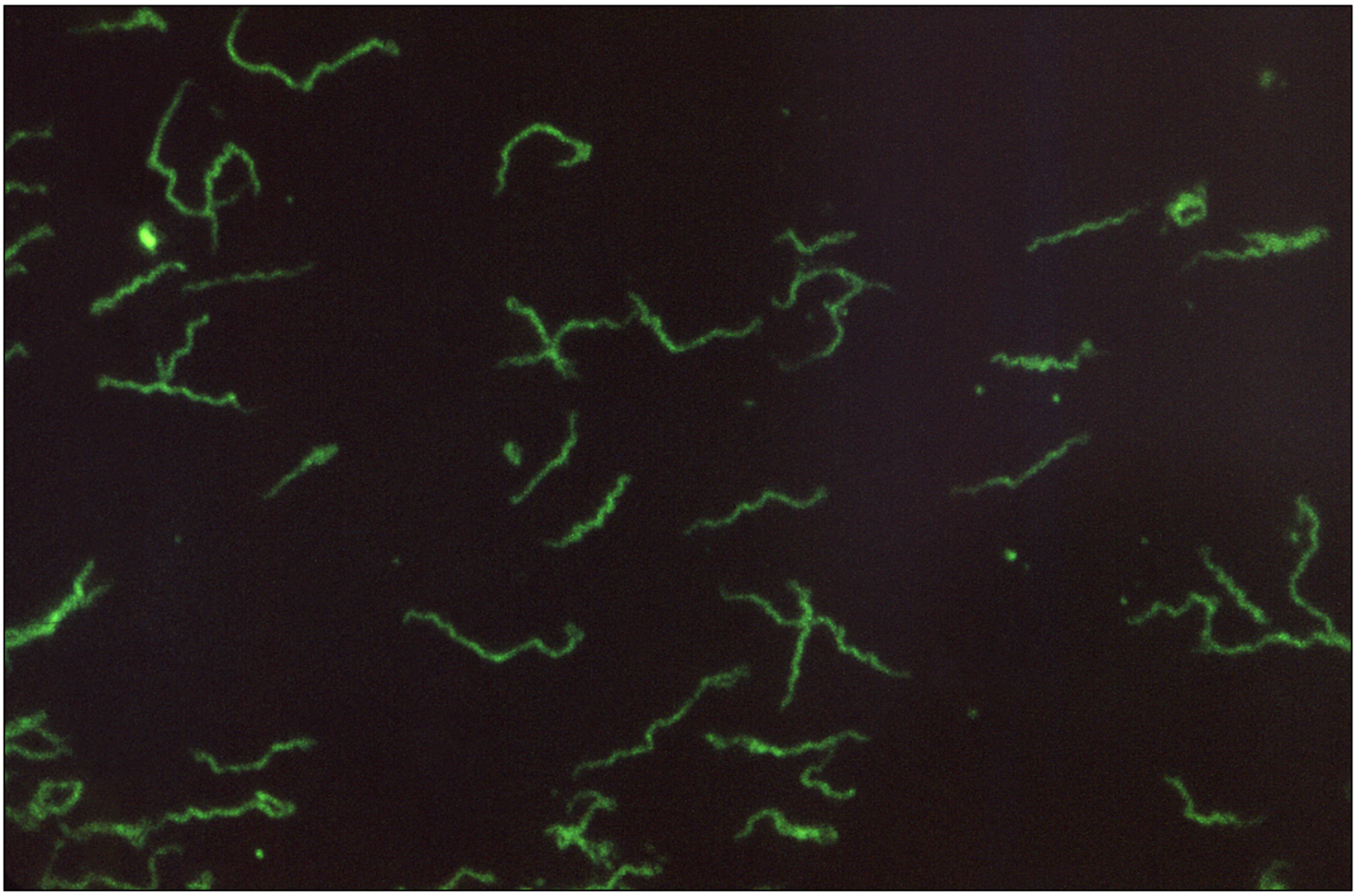

Figure 9 Syphilis Serologic Screening—Reverse Sequence Algorithm

*If the patient is at risk for syphilis, repeat the RPR or VDRL in several weeks. Prozone and biologic false-positive tests should be ruled out.
All positive qualitative nontreponemal tests should reflex to automatically have a quantitative RPR or VDRL titer performed (indicated on figure with dotted line).
Abbreviations: EIA = enzyme immunoassay; CIA = chemiluminescence immunoassays; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = *Treponema pallidum* particle agglutination.

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

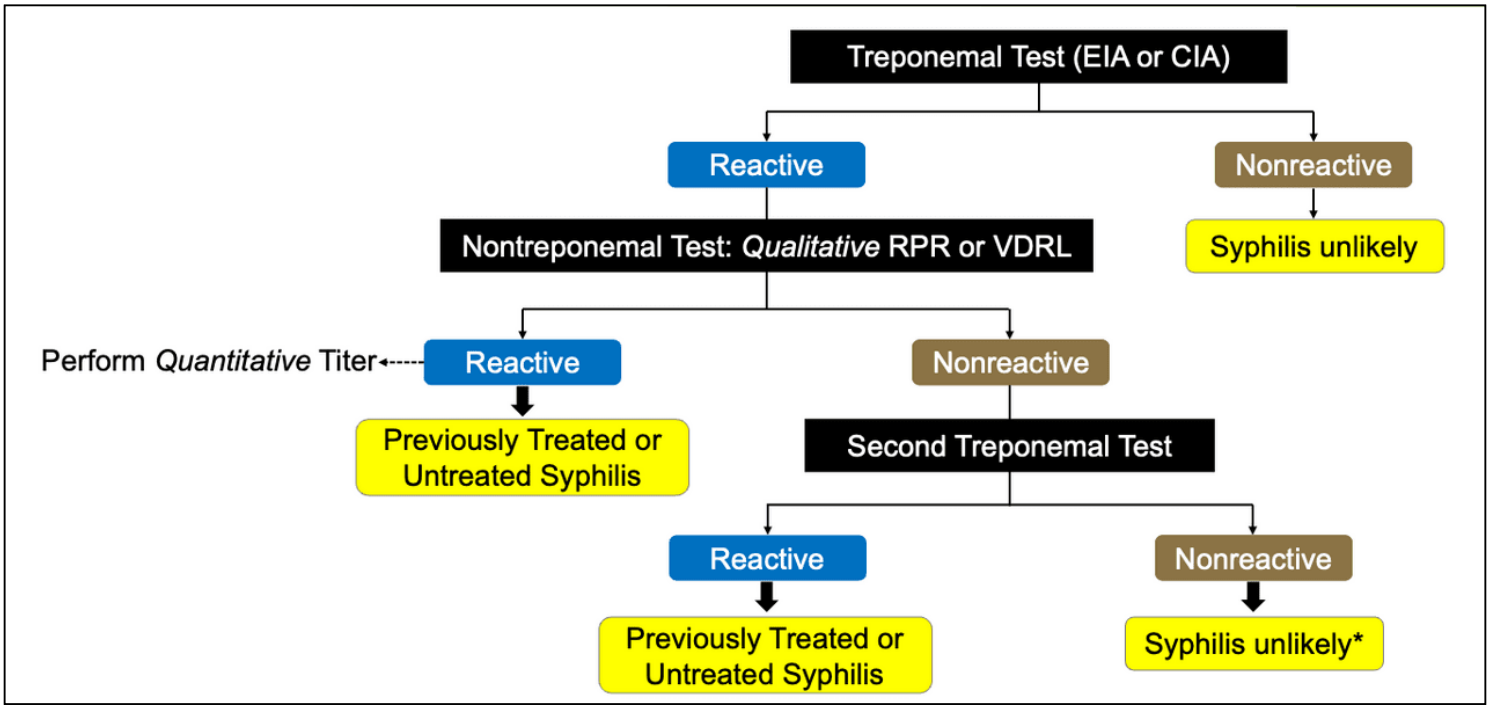

Figure 10 Syphilis Serologic Screening—Traditional Sequence Algorithm

All positive qualitative nontreponemal tests should reflex to automatically have a quantitative RPR or VDRL titer performed (indicated on figure with dotted line).
Abbreviations: RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = *Treponema pallidum* particle agglutination.

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

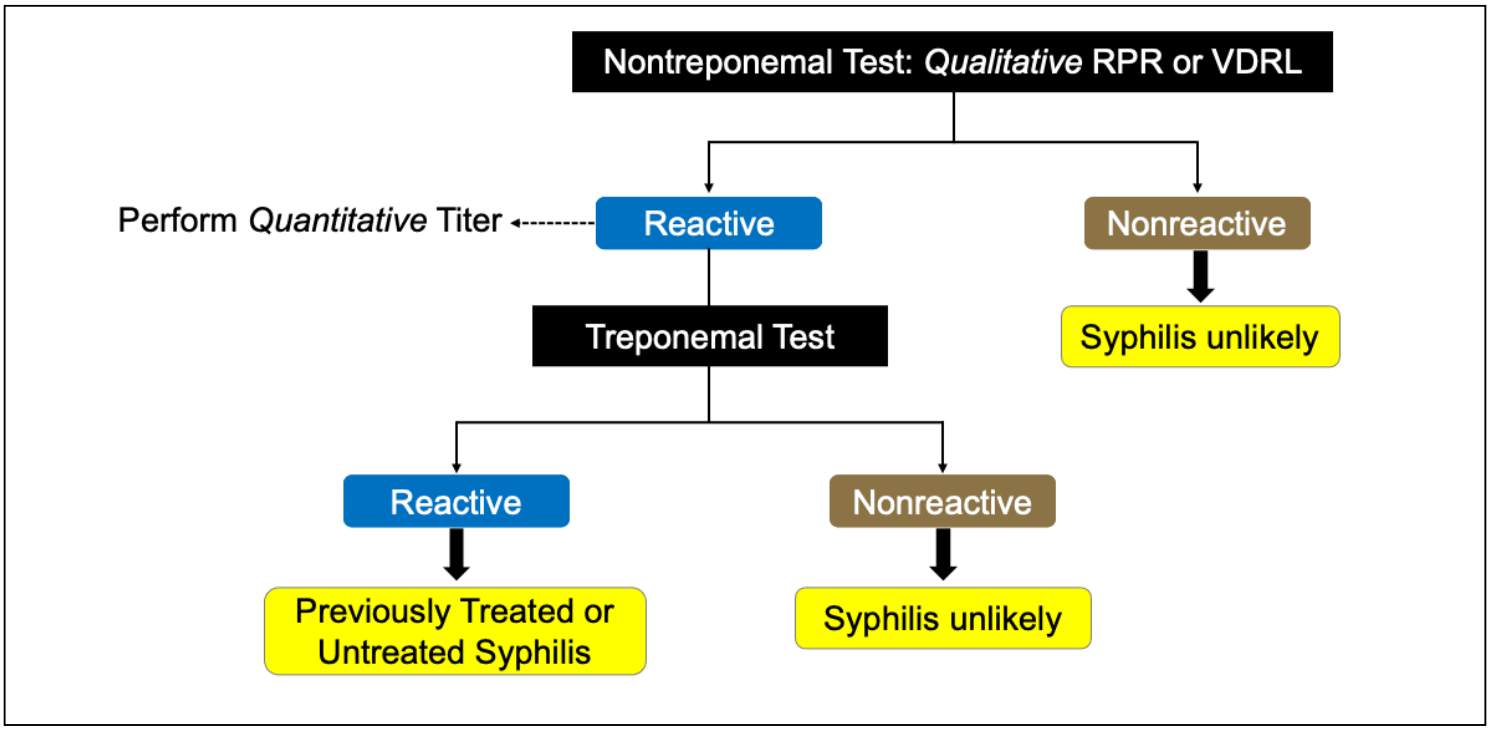

Figure 11 (Image Series) - Examples of Changes in Nontreponemal Titers (Image Series) - Figure 11 (Image Series) - Examples of Changes in Nontreponemal Titers
Image 11A: Examples of Decreases in Nontreponemal Titers

This graphic shows three examples of decreases in nontreponemal titers when comparing two tests. Test number 1 is represented as red and test number 2 as blue.

Illustration by David H. Spach, MD

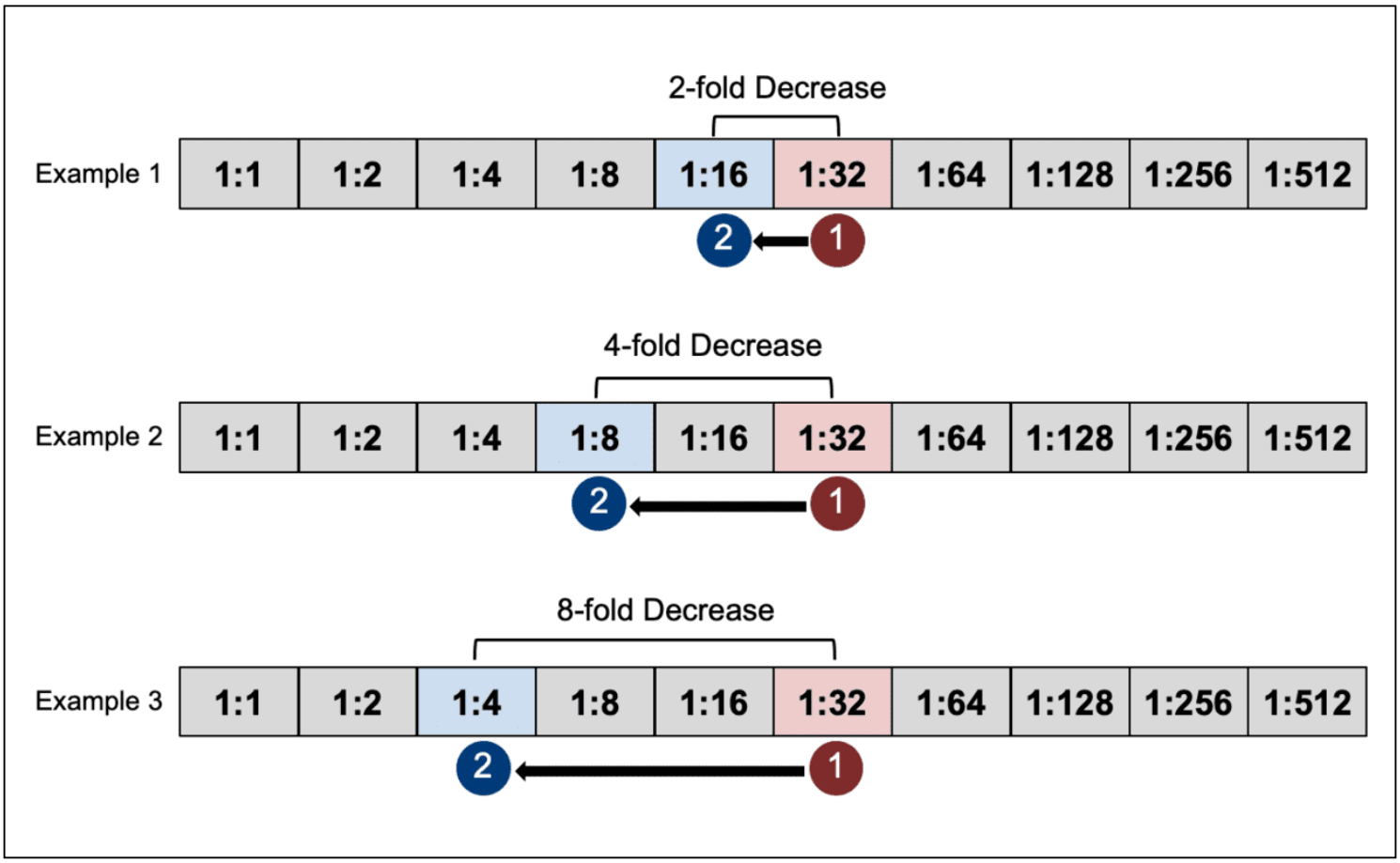

Figure 11 (Image Series) - Examples of Changes in Nontreponemal Titers
Image 11B: Examples of Increases in Nontreponemal Titers

This graphic shows three examples of increases in nontreponemal titers when comparing two tests. Test number 1 is represented as red and test number 2 as blue.

Illustration by David H. Spach, MD

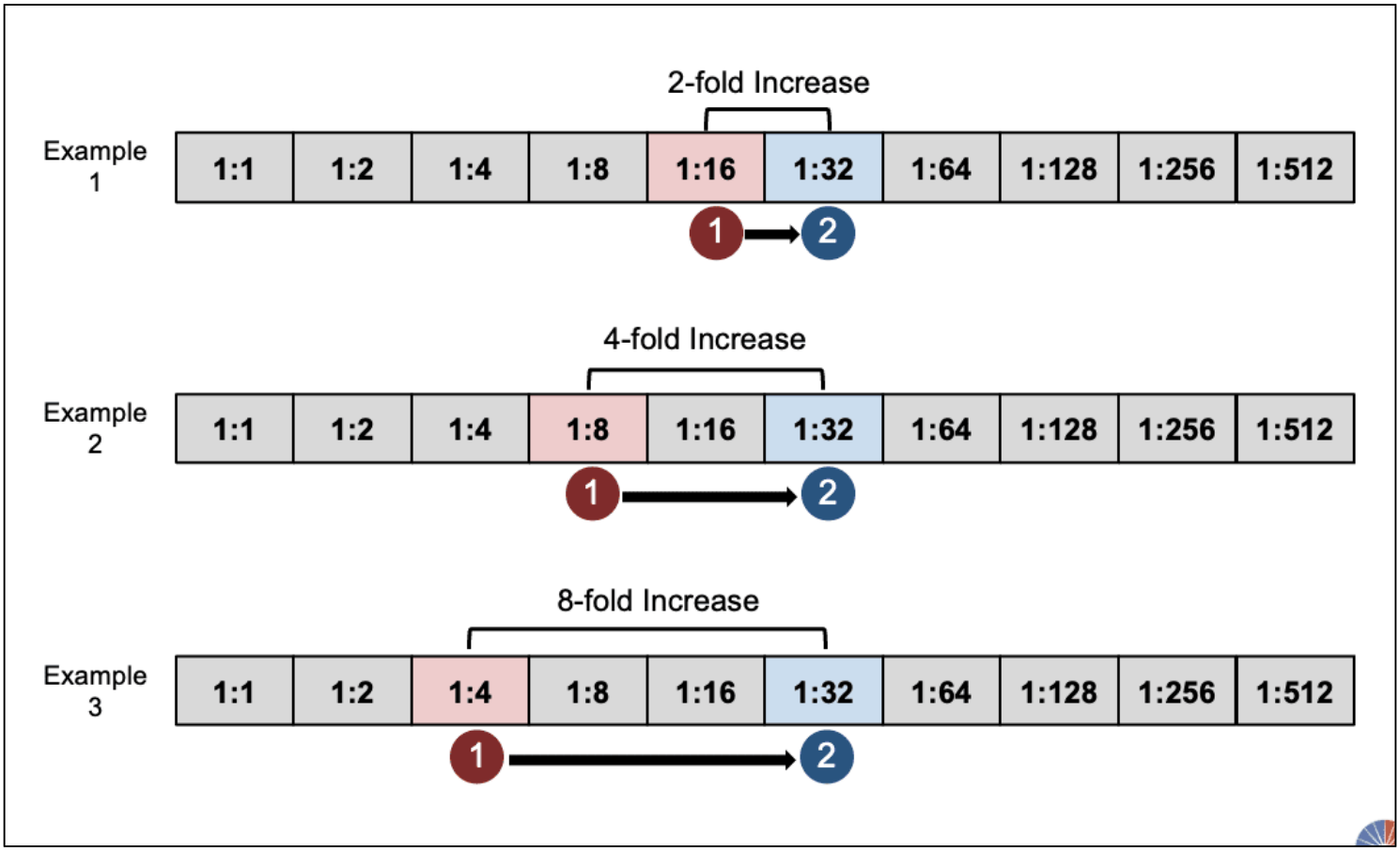

Table 1.

Sensitivity and Specificity of Common Serological Tests in Untreated Syphilis

	Sensitivity During Stage of Infection, % (range)				Specificity, % range
Test	Primary	Secondary	Latent	Late	
VDRL	78 (74-87)	100	96 (88-100)	71 (37-94)	98 (96-99)
RPR	86 (77-99)	100	98 (95-100)	73	98 (93-99)
FTA-ABS	84 (70-100)	100	100	96	97 (94-100)
TP-PA	88 (86-100)	100	100	NA	96 (95-100)
ELISA (IgG)	100	100	100	NA	100

*FTA-ABS and TP-PA are generally considered equally sensitive in the primary stage of disease.

Abbreviations

NA = not available
VDRL = Venereal Disease Research Laboratory
RPR = Rapid Plasma Reagin
FTA-ABS = Fluorescent Treponemal Antibody Absorbed
TP-PA =*Treponema pallidum*-Particle agglutination
ELISA= Enzyme Linked Immunoassay

Source:

- Seña AC, White BL, Sparling PF. Novel *Treponema pallidum* serologic tests: a paradigm shift in syphilis screening for the 21st century. Clin Infect Dis. 2010;51:700-8. [PubMed Abstract]

Table 2. 2021 STI Treatment Guidelines: Syphilis
Treatment of Primary and Secondary Syphilis Among Adults*

*Recommendations for treating syphilis among persons with HIV infection and pregnant women are not addressed in this table.

Recommended Regimen
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy when used to treat primary and secondary syphilis, regardless of HIV status.

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

Table 3. 2021 STI Treatment Guidelines: Syphilis
Treatment of Latent Syphilis Among Adults*

*Recommendations for treating syphilis in persons with HIV and pregnant women are not addressed in this table.

Recommended Regimen for Early Latent Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV status.

Recommended Regimen for Late Latent Syphilis
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

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

Table 4. 2021 STI Treatment Guidelines: Syphilis
Treatment of Tertiary Syphilis Among Adults

Recommended Regimen for Treatment of Tertiary Syphilis with Normal CSF Examination
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin.

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

Table 5. 2021 STI Treatment Guidelines: Syphilis
Treatment of Neurosyphilis, Ocular Syphilis, or Otosyphilis Among Adults

Note: procaine penicillin G is no longer available for use and therefore is not included in this table.

Recommended Regimen
Aqueous crystalline penicillin G *18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days*

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

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

Table 6. 2021 STI Treatment Guidelines: Syphilis
Treatment of Syphilis Among Persons with HIV

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

Recommended Regimen for Treatment of Primary and Secondary Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis among persons with HIV do not result in enhanced efficacy.

Recommended Regimen for Treatment of Early Latent Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*

Recommended Regimen for Treatment of Late Latent or Latent Syphilis of Unknown Duration
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

Recommended Regimen for Treatment of Neurosyphilis, Ocular Syphilis, and Otic Syphilis
Aqueous crystalline penicillin G *18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days*
Note: The duration of the recommended regimen for neurosyphilis is shorter than the duration of the regimen used for treatment of latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of neurosyphilis treatment to provide a total duration of therapy comparable to treatment of latent syphilis.

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