Syphilis in the United States: An Update for Clinicians With an Emphasis on HIV Coinfection

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Diagnosis and treatment of syphilis are challenging because of its variable clinical presentation and course and the lack of definitive tests of cure after treatment. This review of the most recent literature on the epidemiology, clinical manifestations, current diagnosis, and treatment of syphilis is focused toward clinicians who treat patients with this disease. Syphilis coinfection with human immunodeficiency virus is emphasized because it is increasingly common in the United States and affects the initial presentation, disease course, diagnosis, and treatment of syphilis. Of particular consequence is the effect of human immunodeficiency virus on the clinical diagnosis, prevalence, and course of neurosyphilis, one of the most serious consequences of syphilis infection.

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CDC = Centers for Disease Control and Prevention; CNS = central nervous system; CSF = cerebrospinal fluid; FTA-ABS = fluorescent treponemal antibody absorption; HIV = human immunodeficiency virus; MSM = men who have sex with men; RPR = rapid plasma reagin; STD = sexually transmitted disease

Clinicians from large metropolitan areas frequently face the challenge of diagnosing syphilis and treating patients with syphilis. In doing so, they are often faced with questions regarding interpretation of clinical findings and laboratory results and selection of appropriate therapy. Interpretation of the data available to answer these questions is often challenging given the paucity of large well-designed studies and the substantial variability that characterizes the clinical presentation of syphilis. Such a challenge is particularly found in the treatment of patients coinfected with syphilis and human immunodeficiency virus (HIV). To guide clinicians in this difficult task, we discuss the most recent literature on the epidemiology, clinical manifestations, diagnosis, and treatment of syphilis and the corresponding effects of HIV coinfection.

EPIDEMIOLOGY OF SYPHILIS IN THE UNITED STATES AND ITS ASSOCIATION WITH HIV INFECTION

Syphilis has been an important public health problem in the United States throughout the past century. Although the incidence peaked in the United States during the 1940s, subsequent aggressive public health interventions that involved penicillin, case finding, and contact tracing led to a significant decrease in the incidence of primary and secondary syphilis during the following decade (from 66.9 to 3.9 cases per 100,000 persons between 1947 and 1956).[1] Since then, rates have shown recurrent peaks and troughs in approximately 10-year cycles.[1] Although treponemal antigenic variation might account for this cyclic pattern,[2-5] it seems clear that changes in behavior and sexual practices have played a role as well.[6,7] In the late 1970s and early 1980s, one of those epidemics mainly affected gay men and other men who have sex with men (MSM).[1,7] With the appearance of HIV, AIDS-related mortality, and reduced high-risk sexual behavior among gay men and other MSM, syphilis once again became a disease more prominent in heterosexual people at the end of the 1980s and in the early 1990s.[7] The use of crack cocaine in major cities in the United States and the increase of sex in exchange for money or drugs contributed to this change.[1,8] During the mid-1990s, the incidence of syphilis decreased, and most new cases were among low-income heterosexual African American people in the Southern states. Targeting that population, the Centers for Disease Control and Prevention (CDC) implemented the National Plan to Eliminate Syphilis in 1999, which led to a subsequent decline in the incidence of syphilis.[9] Infection reached its lowest point during 2000, when the rate of primary and secondary syphilis was 2.1 cases per 100,000 persons.[9,10]

The recent increase in the male to female syphilis incidence rate ratio suggests an increase in syphilis in gay men and other MSM. Currently, gay men and other MSM bear the major burden of the syphilis epidemic, accounting for 65% of all primary and secondary syphilis cases in the United States.[11] Given that gay men and other MSM from major metropolitan areas had a well-established HIV epidemic, syphilis and HIV coinfection is now increasingly common.[10-13] An estimated 16% of all patients and 28% of

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TABLE 1. **Differential Diagnoses of Genital Ulcer Disease**

Category	Common	Less common
Sexually transmitted diseases	Genital herpes Primary syphilis	Chancroid Lymphogranuloma venereum Granuloma inguinale
Other infections	Cellulitis (*Streptococcus* species and *Staphylococcus aureus*)	Herpes zoster Deep fungi
Allergic reactions	Fixed drug reactions Contact dermatitis	Erythema multiforme Toxic epidermolysis
Autoimmune diseases	Aphthous ulcers Lichen planus	Lupus erythematous Crohn disease Behçet disease Pemphigus Vasculitis Pyoderma gangrenosum
Malignancy	Squamous cell carcinoma Intraepithelial neoplasia	Extramammary Paget disease Basal cell carcinoma Lymphoma or leukemia Histiocytosis X

men infected with syphilis had coinfection with HIV in the United States.[13-15] Similarly, major cities reported that between 20% and 70% of MSM infected with syphilis are coinfected with HIV.[11,16]

One of the major concerns regarding the coexistence of HIV and syphilis in any given population is that syphilis, as with other genital ulcer diseases, might facilitate HIV acquisition and transmission. Genital ulcers can increase HIV acquisition by interfering with the natural mucosal and epithelial barriers[17] and by causing local inflammation.[18-20] Syphilis and other sexually transmitted diseases (STDs) can increase HIV transmission by increasing viral shedding[21,22] and seminal viral load[19,23] in coinfected patients. Furthermore, syphilis has been found to lead to decreased (at least transiently) CD4 T-cell counts and increased plasma viral load in patients chronically infected with HIV,[24-27] both of which have been linked to an increased in HIV transmission.[28] Accordingly, syphilis has been estimated to increase HIV transmission 2- to 9-fold and HIV acquisition 2- to 4-fold.[29]

TABLE 2. **Clinical Manifestations of Select Sexually Transmitted Diseases That Cause Genital Ulcers***

Disease	Characteristics
Primary syphilis (*Treponema pallidum pallidum*)	Painless ulcer with indurated border; typically solitary but can be multiple in HIV-infected patients. Although atypical presentations can be seen, it never presents as vesicles
Genital herpes (herpes simplex virus)	Cluster of shallow small vesicles that evolve into painful ulcers on an erythematous base; constitutional symptoms are common during primary infection
Chancroid (*Haemophilus ducreyi*)	Painful, deep, often necrotizing ulcer with sharp borders and little induration, covered with yellowish exudates; multiple lesions are common
Lymphogranuloma venereum (*Chlamydia trachomatis*)	Painless single papule that may evolve into a superficial ulcer; tender unilateral inguinal lymphadenopathy follows a few weeks later

* HIV = human immunodeficiency virus.

However, despite the increased rates of syphilis and other STDs, no temporal increase in HIV incidence has been detected among gay men and other MSM from cities with well-established HIV epidemics.[12,30,31] Some suggest that the frequent practice of serosorting (finding sex partners with the same HIV serostatus) might explain this stability.[30] However, these stable rates of HIV infection are not reassuring given that increases in STDs in any population may forewarn of future increases in HIV. During the syphilis epidemic that affected the heterosexual population in the 1990s, the distribution of syphilis paralleled the distribution of HIV transmission.[32] Now, rates of primary and secondary syphilis continue to increase among men, ethnic minorities, and, after decreasing for 13 years, women.[10] Furthermore, infected bisexual men could be contributing to the incidence of syphilis among women.[33-35] Together, these increases in the rate of syphilis might presage the spread of HIV into other at-risk populations.

CLINICAL PRESENTATION AND NATURAL HISTORY OF DISEASE

Syphilis is a highly infectious STD caused by infection by *Treponema pallidum pallidum*.[36] Once infection occurs, syphilis is a systemic disease with a wide variety of presentations in which symptomatic periods alternate with periods of clinical latency.[37] Differential diagnoses of genital ulcer disease and the clinical manifestations of the most common STDs are provided in Tables 1 and 2. The clinical

manifestations of syphilis are divided into primary, secondary, latent, and tertiary stages. In general, a 3-week incubation period follows the initial infection, after which an ulcer or chancre (primary syphilis) appears at the site of inoculation (Figures 1 and 2). The chancres may vary greatly in presentation but can often be distinguished from other conditions by the fact that they are painless, nonpurulent, and indurated. Unfortunately, only a third of cases of primary syphilis present with these typical characteristics.[38] Induration is the most common sign and occurs in 47% to 92% of cases.[8] Because chancres are often singular and painless, primary syphilis is often unnoticed, especially in women, gay men, and other MSM in whom the lesions are often located in difficult-to-visualize areas. Regional lymphadenopathy is also common, especially when lesions are present, and may be associated with systemic symptoms. The duration of the primary stage ranges from 3 to 90 days.[8] Although most patients coinfected with HIV and syphilis present in a fashion similar to the general population, larger, deeper, and more numerous chancres that take longer to heal are seen more frequently among coinfected patients (Figures 1 and 2).[39-41]

Secondary syphilis presents as superficial skin and mucous membrane lesions that appear between 4 and 10 weeks after infection. In the general population, this stage overlaps the primary syphilis stage in approximately one-third of patients.[8] However, in HIV-coinfected patients, primary and secondary syphilis overlap in up to 75%.[39] Secondary syphilis is classically characterized by a nonpruritic rash and/or generalized lymphadenopathy (Figures 3 and 4). The rash is typically associated with systemic symptoms and can mimic many other dermatological conditions. Nevertheless, the rash in early secondary syphilis is characteristically macular and often consists of many 5- to 10-mm red or copper-colored macules. Lesions most often affect the trunk and limbs and are found on the palms and soles in 50% to 80% of cases.[39,40] The rash in later secondary syphilis may take many forms (papular, papulosquamous resembling psoriasis) but will not be vesicular. Although highly unusual, malignant secondary syphilis—an aggressive ulcerating form of secondary syphilis—has been described to be more frequent during advanced HIV disease.[42,43] As with primary syphilis, secondary syphilis resolves without treatment, although approximately one-quarter of untreated patients (particularly during the first year after infection) will have recurrences.[37]

Secondary syphilis is followed by a period termed *latent syphilis* in which no symptoms are present, and diagnosis can be achieved only through serological testing. Latent syphilis is subdivided into early latent (if the infection was acquired within the preceding year) and either late latent or latent syphilis of unknown duration. The distinction is useful inasmuch as those with early syphilis are considered potentially infectious because of the greater probability of experiencing relapse to secondary syphilis.[37] Because of the lack of lesions, patients with late latent syphilis are generally not considered infectious to sex partners. However, the possibility of vertical transmission is the reason for routine syphilis screening of all pregnant women. Although cure without treatment is questioned, many patients will remain in this latent phase indefinitely. Up to 25% of patients with untreated syphilis will eventually develop tertiary manifestations of syphilis.[37]

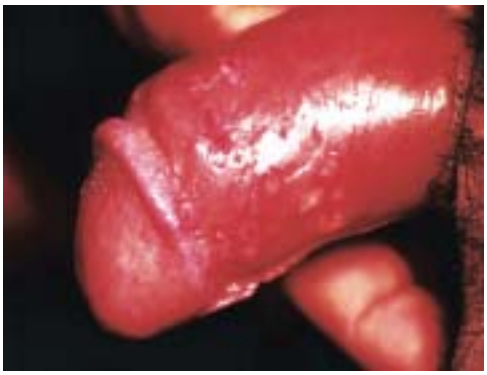

FIGURE 1. Multiple chancres seen in patients with human immunodeficiency virus presenting with primary syphilis.

Tertiary syphilis describes a broad range of manifestations but most commonly includes cardiovascular, gummatous, and/or neurological effects. Together, approximately 15% to 40% of individuals who are not treated will develop tertiary manifestations, with men at increased risk compared with women.[8,37] Cardiovascular complications are the most common of the effects and typically present within 10 to 30 years of infection.[37,44] They often involve the aortic arch and can lead to angina from coronary ostitis, aortic regurgitation, or aortic aneurysm. Gummatous syph-

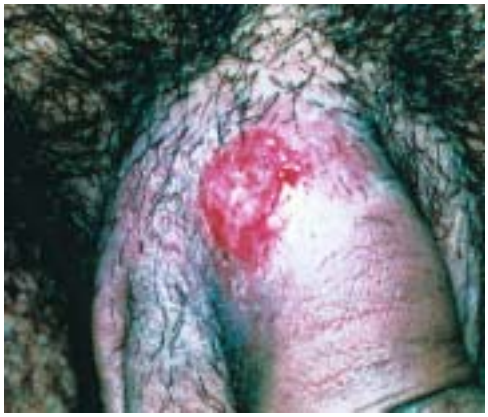

FIGURE 2. Typical chancre of primary syphilis.

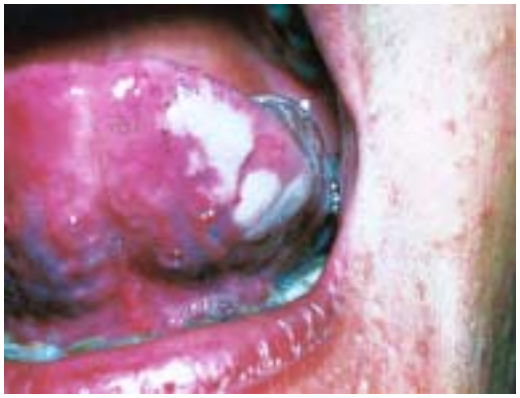

FIGURE 3. Mucous patches confused with oral candidiasis in a patient with human immunodeficiency virus.

ilis is often referred to as benign late syphilis because it is rarely physically debilitating. Nevertheless, depending on the site of the lesion(s), it can lead to serious complications. Gummas can present in any organ and can lead to complications, including ulcers of the skin, collapse of the palate or nasal septum, or organomegaly. Gummas can develop any time after a year of infection, but incidence peaks at approximately 15 years.[8,37,44] The most severe effects of untreated syphilis infection are those that involve infection of the central and peripheral nervous system (neurosyphilis) and are discussed later in this article.

Fewer data are available on the effect of syphilis on the progression of HIV infection. Infection with *T pallidum* has been shown to transiently decrease CD4 T-cell counts in HIV-infected patients[21,22,45-47] and to induce lymphocyte and CD4 apoptosis.[48] However, it is unknown whether these changes are different from those in patients without HIV infection in whom a decrease in CD4 T-cell percentage has also been found during syphilis or whether these transient changes affect the overall course of the HIV disease. Similarly, syphilis has been found to increase HIV viral load,[21,22,45,46] but whether these increases are associated with development of resistance or accelerated disease progression is unclear.[49] Although the implications of these transient changes in the long-term course of the HIV infection are unknown, clinicians should be aware that syphilis and other asymptomatic STDs might account for otherwise unexplained decreases in CD4 T-cell counts or increases in plasma viral load of HIV-infected patients. Prompt STD risk assessment and screening are indicated in this scenario.

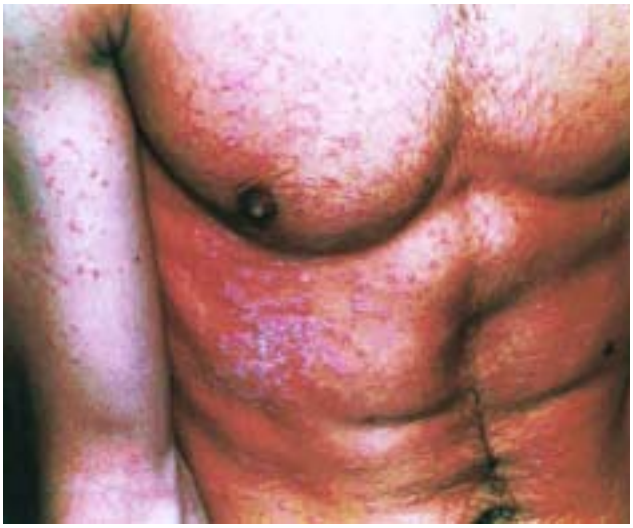

FIGURE 4. Secondary syphilis.

NEUROSYPHILIS

The clinical presentations of neurosyphilis are extremely varied and, for practical purposes, can be divided into early and late neurosyphilis.[50] Early neurosyphilis refers to the direct or indirect neurological manifestations of syphilis during the early stages of the disease (primary, secondary, or early latent syphilis). Clinical presentations of early neurosyphilis are a reflection of the increased frequency of meningeal and blood vessel compromise and include meningovascular diseases (eg, meningitis, strokes, seizures), acute and subacute myelopathy, brainstem or cranial nerve abnormalities, and vestibular and ocular disease. Although overlap can be substantial, late neurosyphilis refers to the neurological manifestations associated with chronic syphilis. Late neurosyphilis tends to affect the brain and spinal cord parenchyma, typically presenting as dementia, tabes dorsalis, general paresis, sensory ataxia, or bowel or bladder dysfunction.

After infection, treponemal invasion of the cerebrospinal fluid (CSF) occurs in approximately 25% of patients. However, most patients, including HIV-coinfected patients, will have spontaneous resolution of the central nervous system (CNS) invasion even in the absence of treatment.[51] If the immune system is not able to control the infection, asymptomatic or symptomatic early neurosyphilis occurs.[52] In both asymptomatic and symptomatic cases, CSF abnormalities can be seen during this period. The increased frequency of CSF abnormalities in HIV-infected patients at baseline[52,53] makes the diagnosis of neurosyphilis and interpretation of CSF results even more difficult.[54,55]

The management of neurosyphilis in an HIV-infected patient is controversial. Early reports suggest that HIV infection accelerates and changes the course of neurosyphilis.[56,57] In contrast to patients who do not have HIV, most new cases of early neurosyphilis in HIV-infected individu-

als are identified at the initial presentation, and several authors have documented that in certain patients conventional treatment with penicillin G benzathine for primary or secondary syphilis might not be effective in preventing CNS progression in HIV-infected patients.[58,59] This finding led some experts to recommend that, in all HIV-infected persons with early syphilis, the CSF should be examined before treatment and after treatment if abnormalities are found.[56] However, the interpretation of CSF findings in the setting of HIV infection is particularly problematic. Although higher cell counts, higher protein levels, and lower glucose levels in CSF were found in HIV-infected patients with syphilis, the clinical and prognostic importance of such abnormalities remains unknown.[60] Furthermore, no benefit of treating asymptomatic laboratory-defined neurosyphilis was found in the only prospective randomized trial that tried to assess that topic.[61]

Ocular syphilis might be more frequent among HIV coinfected patients than initially expected.[62] Several studies, primarily from tertiary referral centers, have suggested a prevalence of ocular syphilis as high as 10% of HIV-infected patients who present with syphilis and ocular symptoms.[63-65] Given this unexpectedly high prevalence, ocular syphilis should be considered in any HIV-infected patient who presents with visual symptoms, irrespective of the patient's CD4 T-cell count. Every patient with syphilis and visual symptoms should be referred to the ophthalmologist for a formal evaluation for ocular disease. Importantly, ocular syphilis should always be considered a potential manifestation of neurosyphilis, and all such patients should undergo a complete neurological examination, including CSF analysis.

In light of the problems in interpreting the clinical implications of laboratory data, how should clinicians diagnose neurosyphilis in HIV-infected patients? Unfortunately, no single test is available to diagnose neurosyphilis. All patients with syphilis who undergo lumbar puncture should undergo CSF biochemical tests, blood cell count measurements, and VDRL tests. Some experts recommend performing a fluorescent treponemal antibody absorption (FTA-ABS) test on CSF as well. Although insensitive, a CSF VDRL test is highly specific for neurosyphilis; thus, when the result is reactive in the absence of substantial contamination of CSF with blood (ie, red blood cell count >2000/mm^3), it is considered diagnostic of neurosyphilis. The current CDC guidelines recommend that patients with an elevated CSF leukocyte count (>5 white blood cells/mm^3) should also be considered to have neurosyphilis. However, given that many HIV-infected patients will have some degree of pleocytosis at baseline, many experts recommend using a white blood cell threshold of 20/mm^3 to diagnose neurosyphilis in HIV-coinfected patients. A normal CSF white blood cell count rules out neurosyphilis. The CSF FTA-ABS test is a highly sensitive test and can yield false-positive results. Although the interpretation of a positive result is difficult, some experts suggest that a negative CSF FTA-ABS test result can be used to exclude neurosyphilis. A high CSF protein level aids in the diagnosis of neurosyphilis but is not diagnostic by itself.

Currently, the CDC recommends a CSF examination in any patient with syphilis and neurological or ophthalmic signs or symptoms, evidence of active tertiary syphilis, treatment failure, or HIV infection with late latent syphilis or syphilis of unknown duration.[60] Some experts suggest that other groups of HIV-infected patients coinfected with syphilis might also benefit from a lumbar puncture.[66] In 2 recent studies, a nontreponemal serological titer of 1:32 or higher was found to be associated with an abnormal CSF finding suggestive of neurosyphilis in HIV coinfected patients.[67,68] In one of those studies, a CD4 T-cell count less than 350/μL was also predictive of similar CSF abnormalities.[68] In our practice, we do not recommend CSF examination in HIV-infected patients with early syphilis (ie, primary, secondary, or early latent) who lack neurological, ocular, or otologic signs or symptoms, regardless of CD4 T-cell count or nontreponemal serological titers.

DIAGNOSIS OF SUSPECTED SYPHILIS

When attempting to diagnosis the condition of a patient with suspected syphilis, a detailed history and physical examination are mandatory. During the interview, a risk assessment for STDs that includes direct ascertainment of sexual practices and questioning regarding symptoms of syphilis that include dermatological, neurological, ocular, auditory, and vestibular manifestations should be particularly emphasized. Careful examination of the skin, scalp (ie, patchy alopecia), oropharynx, and genital and anal area, as well as a complete neurological examination, should be performed in every patient. When lesions suggestive of syphilis are present, confirmation by direct visualization of the treponemes by darkfield microscopy or direct fluorescent antibody is recommended. Unfortunately, darkfield microscopy is relatively insensitive (75%-95%, depending on the skill of the investigator), requires special equipment and training, and is not suitable for oral or rectal samples because of the potential presence of nonpathogenic spirochetes in those sites. Furthermore, it is only useful during the primary and secondary stages of infection. In selected cases, biopsy of suspicious lesions may be indicated. When a biopsy is performed, immunological staining is preferred given its greater sensitivity and specificity over silver staining.[69]

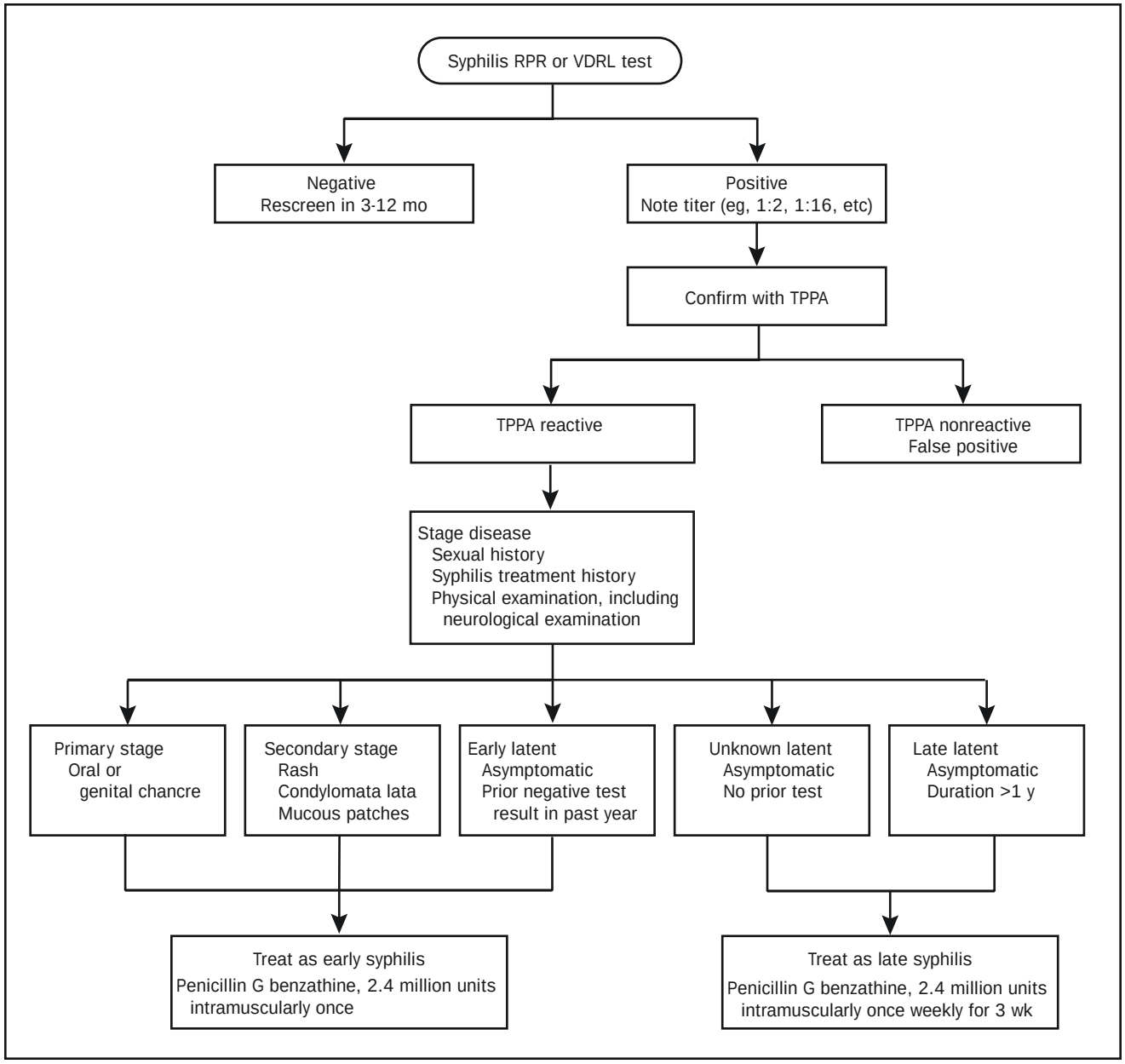

FIGURE 5. Diagnostic algorithm based on serological test results. Fluorescent treponemal antibody absorption test is another treponemal assay often used. A rapid plasma reagin (RPR) or VDRL titer of 1:16 or greater suggests infection in the prior year. TPPA = *Treponema pallidum* particle agglutination.

Interpretation of Serological Test Results at the Time of Diagnosis

Serological testing is the current standard for syphilis diagnosis, and all patients with suspected syphilis should undergo this testing. Most syphilis is diagnosed with a 2-stage testing process that includes nontreponemal testing as the initial screen and treponemal tests to confirm diagnosis (Figure 5). The 2-step approach is useful in limiting false-positive test results. Nontreponemal testing uses the reactivity of human IgG and IgM antibodies to *T pallidum* with the synthetic cardiolipin-lecithin-cholesterol antigen. The most commonly used nontreponemal tests are the rapid plasma reagin (RPR) and the VDRL test. Treponemal testing refers to tests that use *T pallidum* antigens. The diagnosis and interpretation of both treponemal and nontreponemal serological tests should be the same in HIV-infected patients and in the general population. Rare cases of false-negative nontreponemal test results have

been reported among HIV-infected patients coinfected with syphilis.[70] More frequently, however, higher than expected serological titers are reported among HIV-infected patients, sometimes leading to a prozone effect (antibody excess resulting in small antigen-antibody complexes that do not clump to form visible agglutination or a reactive test).[71-74]

Interpretation of Serological Test Results During Follow-up

Nontreponemal Serological Tests. Without treatment, nontreponemal antibody titers will peak during secondary syphilis and then will gradually decline even in the absence of treatment.[61] Without treatment, approximately 30% of patients with syphilis from the general population will become seronegative for nontreponemal antibodies during their lifetime. In the setting of treatment, nontreponemal titers decrease faster, and most patients will become seronegative within 1 year. Because of the faster decrease in nontreponemal titers that follows appropriate treatment and the lack of a single test to confirm syphilis cure, a 4-fold or 2-dilution decrease in serological titer (eg, a decrease from 1:16 to 1:4) is traditionally considered a satisfactory serological response. Given that RPR titers tend to be higher than VDRL titers, using the same nontreponemal test for diagnosis and follow-up is recommended. However, in a recent prospective randomized trial, Rolfs et al[61] found that RPR titers failed to decrease by 2 or more dilutions in 17% and 14% of the patients at 6 and 12 months, respectively.

The natural course of nontreponemal titers after treatment of HIV-infected patients has been more variable. Patients with HIV infection might take longer to experience serological improvement after recommended therapy.[41,60,75-78] However, since most of these patients are also at risk of subsequent reinfection, it is difficult to determine whether a steady titer is due to new infection, reaction from a partially treated infection, or immunosuppression.[79] In addition, HIV-infected patients with a prior history of syphilis will have titers that decline much more slowly.

Treatment failure is defined as recurrence of symptoms or signs at any time and/or lack of a 4-fold decrease in nontreponemal titers by the end of the recommended follow-up period (eg, 6-12 months after treatment of early syphilis). Some experts also consider partial response in patients who, despite having a 4-fold decrease in nontreponemal titers, have titers that remain higher than or equal to 1:64. In the general (non–HIV-infected) population, we recommend considering treatment failure if the nontreponemal titers have not decreased at least 4-fold at 6 months of follow-up after treatment of early syphilis or at 12 months after treatment of late syphilis (Figure 6). However, given the slower decline in nontreponemal titers among HIV-infected patients, we recommend monitoring nontreponemal titers for 12 months after the treatment of early syphilis and for 24 months after the treatment of late syphilis before considering treatment failure (Figure 6). Treatment failure is an indication for CSF examination to rule out neurosyphilis, and appropriate retreatment is indicated in all patients.

Reinfection is usually indicated by a documented decrease in nontreponemal titers followed by an increase in such titers. Recurrences of lesions of primary syphilis are usually an indication of reinfection as well. Recurrences of lesions of secondary syphilis could represent reinfection or treatment failure and should be interpreted more cautiously. Reinfection is not necessarily an indication for CSF examination. Most of these cases should be managed as a new case of early infection. However, if doubt exists regarding whether the infection is treatment failure or reinfection, then performing a lumbar puncture to rule out sequestered CNS infection is indicated.

Treponemal Serological Tests. The interpretation of treponemal test results is usually more straightforward. Most patients who had syphilis will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, up to 25% of both HIV-infected and uninfected individuals can revert to being serologically nonreactive 2 to 4 years after treatment.[80-83] In HIV-infected patients, this does not seem to correlate with disease stage or CD4 T-cell count.

New Technologies. Although the serological tests for syphilis help in the diagnosis of syphilis, the inability to rule out syphilis is still a great limitation of current diagnostic tests. Even after the use of molecular techniques, a large percentage of genital ulcers remain undiagnosed,[84] and direct testing methods (biopsy of a lesion, darkfield examination, or direct fluorescent antibody staining of lesion material) to confirm a diagnosis should be considered when serological test results are negative. New treponemal tests that are faster and less expensive are also being developed for use in low-prevalence populations and resource-poor environments.[85-90] Unfortunately, despite the fact that many of these rapid treponemal tests have shown great performance and potential for rapid, point-of-care screening, manufacturers have not sought Food and Drug Administration clearance.

An enzyme immunoassay–based nontreponemal test (SpiroTek Reagin II EIA, Organon Teknika, Durham, NC) was recently found to be more sensitive (93% vs 86%) and equally specific compared with a traditional RPR test.[79] Contrary to all the nontreponemal tests currently available, the enzyme immunoassay test allows for automation, enabling the screening of a large number of samples. Similarly, an antigen-based chemiluminescence immunoassay is being

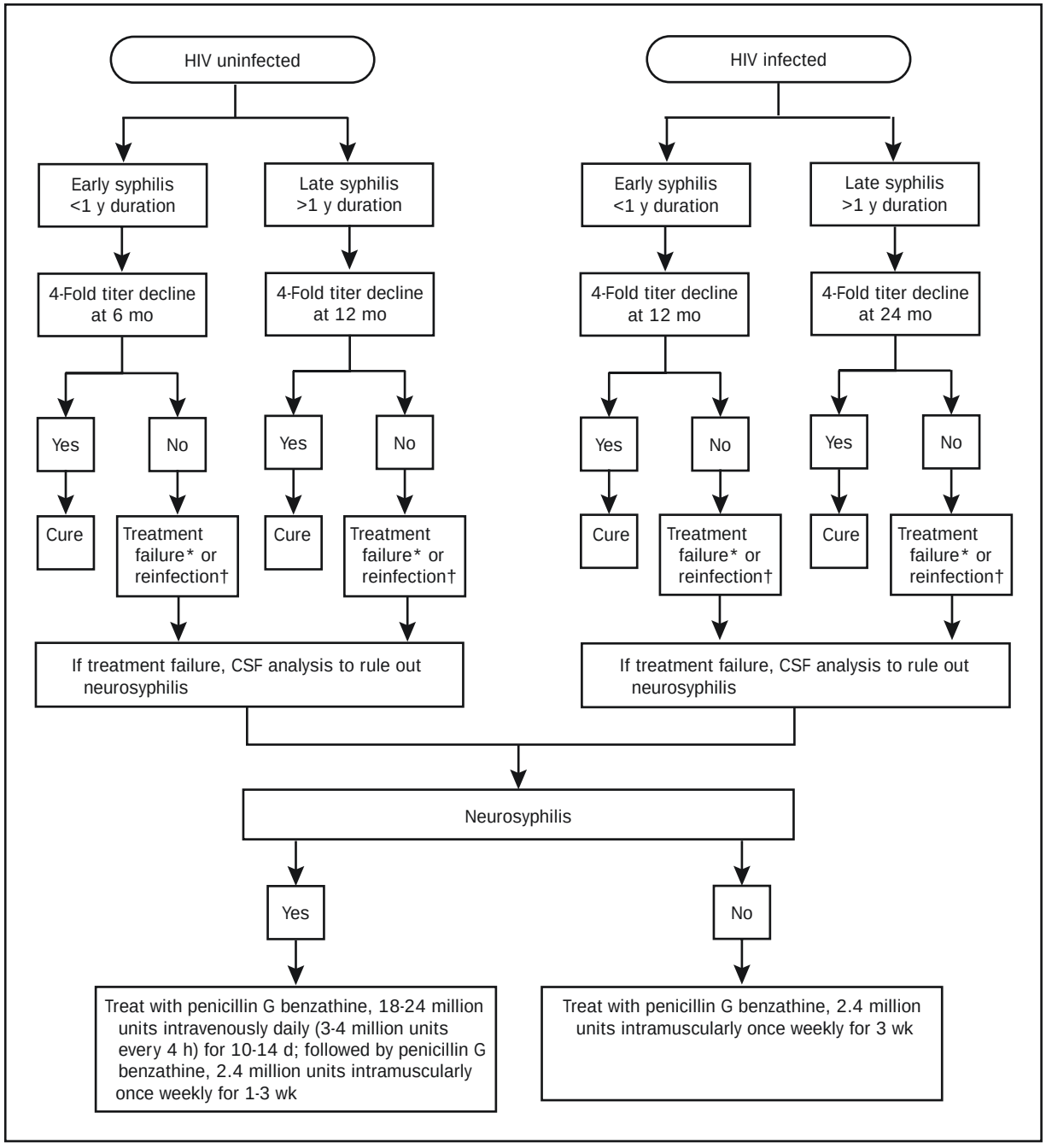

FIGURE 6. Evaluation of serological treatment response algorithm. CSF = cerebrospinal fluid; HIV = human immunodeficiency virus.
*Treatment failure may be caused by untreated neurosyphilis.
†Reinfection may be consistent with a 4-fold serological titer decline followed by a 4-fold serological titer increase and reexposure. Treat with pencillin G benzathine, 2.4 million units intramuscularly once.

successfully used for the diagnosis of syphilis in clinical specimens in blood banks but has not yet been tested in other settings.[91] Western blot and polymerase chain reaction in clinical specimens have also shown higher sensitivity and specificity compared to serological testing and are promising as a confirmatory test for syphilis.[92,93] A multiplex polymerase chain reaction test designed to detect herpes simplex virus, chancroid, and syphilis in genital ulcer disease has had promising results in other countries and research studies, but there is no plan to market it in the United States.[94]

TABLE 3. **Recommended Treatment of Syphilis**

Disease type	Recommended treatment	Alternative treatment*
Primary, secondary, or early latent syphilis	Penicillin G benzathine, 2.4 million units in a single intramuscular dose	Doxycycline, 100 mg orally twice daily for 14 d, or ceftriaxone, 1 g intramuscularly daily for 8-10 d
Late latent syphilis, syphilis of unknown duration, or tertiary syphilis	Penicillin G benzathine, 2.4 million units intramuscularly weekly for 3 consecutive wk†	Doxycycline, 100 mg orally twice daily for 28 d
Neurosyphilis, syphilitic eye disease, or syphilitic auditory disease	Aqueous crystalline penicillin G, 18-24 million units daily (administered every 4 h or by continuous infusion) for 10-14 d followed by penicillin G benzathine, 2.4 million units intramuscularly weekly for 1-3 wk‡	Procaine penicillin, 2.4 million units intramuscularly daily, plus probenecid, 500 mg every 6 h, both for 10-14 d, followed by penicillin G benzathine, 2.4 million units intramuscularly weekly for 1-3 wk‡

*Alternative regimens have not been well studied in patients infected with human immunodeficiency virus.
†If more than 14 days lapse between doses, the series needs to be reinitiated.
‡Recommended by some experts.

TREATMENT

Penicillin G benzathine continues to be first-line therapy for all stages of syphilis (Table 3). Recommended regimens were designed to be bactericidal for sustained periods, and although their use continues to be based on observational data rather than experimental trials, a long history of success and extensive experimental animal studies are available to support their use in HIV-uninfected patients. Three penicillin G benzathine formulations are currently available in the United States: Bicillin L-A (which contains 2.4 million units of penicillin G benzathine), Bicillin C-R (a mixture of 1.2 million units of penicillin G benzathine and 1.2 million units of procaine penicillin), and Bicillin C-R 900/300 (a mixture of 0.9 million units of penicillin G benzathine and 0.3 million units of procaine penicillin), but only Bicillin L-A is currently indicated for the treatment of primary, secondary, and early latent syphilis. The effectiveness of the other formulations remains largely unknown, and these formulations should not be used to treat syphilis. All patients receiving treatment for syphilis should be warned regarding the possibility of developing a Jarisch-Herxheimer reaction. Usually occurring between 2 and 24 hours after treatment, this reaction has been reported more frequently among HIV-infected patients (22% vs 12%).[61] Treatment is largely supportive.

Treatment of Patients With Partial Response, Treatment Failure, and Reinfection

Despite the fact that *T pallidum* remains highly susceptible to penicillin, treatment failure can occur. The rarity of complications of syphilis and the lack of definitive criteria for cure have prompted the use of a 4-fold decrease in nontreponemal titers at 6 to 12 months as supportive evidence of successful treatment. Patients who have an appropriate serological response and are asymptomatic after treatment should be considered cured. Increasing titers after appropriate treatment usually suggest reinfection. However, given that previous syphilis infections, new infections, and individual host factors affect nontreponemal titers, the clinical importance of a lack of an appropriate decline in those titers remains unknown. Nevertheless, all patients with syphilis should have nontreponemal titers checked at 6 and 12 months. Because of potential increased failure rate and progression to neurosyphilis, all HIV-infected patients with syphilis should have nontreponemal titers checked at 3, 6, 9, 12, and 24 months after initial treatment. For patients diagnosed as having and treated for latent syphilis, current guidelines recommend follow-up at 6, 12, 18, and 24 months. If lumbar puncture is performed and the results are abnormal, the procedure should be performed again at 6 months. If nontreponemal titers do not decline 4-fold, if there is a 4-fold increase, or if signs or symptoms persist or recur, treatment is considered to have failed. In those cases, CSF should be sampled, and treatment should be administered as in HIV-uninfected patients (weekly injections of penicillin G benzathine, 2.4 million units intramuscularly for 3 weeks, unless CSF examination indicates neurosyphilis). If additional follow-up cannot be ensured, additional treatment is recommended.[72]

Treatment of Patients Allergic to Penicillin

Most patients with early syphilis who are allergic to penicillin should receive doxycycline, 100 mg orally twice a day for 14 days. If the allergy is not believed to be an anaphylactic reaction, ceftriaxone, 1 g/d intramuscularly for 8 to 10 days, is an alternative. For late syphilis, doxycycline, 100 mg orally twice a day for 28 days, is the recommended treatment. Pregnant women with syphilis who are allergic to penicillin are a notable exception to this indication; these patients should always be admitted to the intensive care unit and desensitized for penicillin treatment.

With minor differences, the recommended treatment and outcome of HIV-infected and uninfected patients are similar.[95,96] Among HIV-infected patients, the lack of appropriate decline in the titers has been the basis for pre-

sumed increased rates of therapeutic failure. Recently, ceftriaxone was suggested as an alternative to penicillin, but high failure rates were seen in HIV-infected patients.[60,97,98] Similarly, the use of azithromycin as an alternative treatment of primary and secondary syphilis is not currently recommended because of high levels of treatment failure due to azithromycin-resistant *T pallidum* found in major cities.[97-99]

Given the high infectivity of early stages of syphilis, all sex partners of patients diagnosed as having syphilis should be presumed to have incubating syphilis and therefore treated accordingly (penicillin G benzathine, 2.4 million units intramuscularly) if they were exposed within the 3 months preceding the diagnosis of the partner's condition. Those exposed more than 90 days before diagnosis should be tested and treated if the serological test results are positive or treated presumptively if results are unavailable or if follow-up is uncertain.

PUBLIC HEALTH INTERVENTIONS

The 3-week average incubation period of syphilis provides an opportunity to locate and treat exposed partners before they become infected and potentially infectious to others. Therefore, identification of recent cases and partner notification have the potential to stop the spread of the epidemic.[100] In all states, syphilis is a reportable disease, and most laboratories report reactive titers directly to local public health agencies.

Serum antibodies against syphilis are not protective, and reinfection can occur at any time; thus, screening high-risk populations continues to be useful to detect new cases.[101] A high rate of asymptomatic STDs has been found among HIV-infected patients in primary care, and routine screening is effective in detecting early asymptomatic syphilis in outpatients.[102-104] The CDC currently recommends that all HIV-infected patients be screened for syphilis and other STDs every 3 to 6 months.[105-107] In practice, we recommend that clinicians who provide care to gay men and other MSM in major cities perform a syphilis screening test with every CD4 T-cell count or HIV plasma viral load assay.

CONCLUSION

Increasing high-risk sexual behavior, particularly among HIV-infected gay men and other HIV-infected MSM, has prompted an increase in rates of syphilis and HIV coinfection. Most HIV-infected patients with syphilis will have similar clinical presentations and should receive treatment similar to that for the general population. Until more data become available, neurosyphilis should be considered in all HIV-infected patients with syphilis, and a lumbar puncture should be performed in patients with neurological manifestations, long-standing syphilis, or treatment failure. Close follow-up and serological testing are recommended for all patients. The evaluation of innovative public health strategies to reduce behavioral and community-level risk factors and further research into the biological interaction between syphilis and HIV infection should enhance syphilis control and our understanding of these important diseases.

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