Managing Syphilis in the HIV-infected Patient

Christopher S. Hall, MD, MS, Jeffrey D. Klausner, MD, MPH, and Gail A. Bolan, MD*

Address
*University of California San Francisco, Sexually Transmitted Disease Control Branch, California Department of Health Services, 1947 Center Street, Suite 201, Berkeley, CA 94704, USA.
E-mail: chall@dhs.ca.gov

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Syphilis has re-emerged in the United States and elsewhere, and clinicians caring for HIV-infected patients are challenged with syphilis diagnosis and management decisions. HIV alters the natural history of syphilis to an extent that is poorly understood, and initial presentation may be more varied in coinfected patients. Although commonly available diagnostic assays for syphilis should be interpreted as usual, such tests rely on antibody measurement and may be an imperfect indicator of active infection. Assessment of all available clinical and risk behavior data remains critically important in the diagnosis of syphilis in coinfected patients. Treatment of syphilis in such patients requires stage-appropriate therapy, with careful serologic monitoring to assess response. Clinicians must have heightened appreciation of the role of frequent risk assessment, serologic screening, symptom recognition, and follow-up of treated patients, as well as an understanding of public health functions such as sex partner treatment and communicable disease reporting.

Introduction

Sir William Osler once declared, "He who knows syphilis, knows medicine." Aptly described as "the great imitator," *Treponema pallidum* subspecies *pallidum* has successfully evaded eradication in the new millennium. In this era, coinfection with HIV has further challenged our management of this complex spirochetal disease. This article addresses key issues in the management of syphilis in the HIV-infected patient and summarizes the latest evidence useful in guiding clinical decision-making.

Epidemiology of HIV/ *Treponema pallidum* Coinfection

The interrelationship between genital ulcer disease (GUD), including syphilis, and the risk for HIV infection is well-documented [1–4]. Syphilis may increase the rate of HIV acquisition between two- and four-fold and the risk for transmitting HIV between two- and nine-fold [1]. Explanations include behavioral factors as well as pathogenetic mechanisms, such as facilitation of HIV transmission caused by syphilis-associated ulceration and inflammation [4].

End of an era: the recent resurgence of syphilis

Despite significant decreases in syphilis incidence in the United States over the past decade, as well as the US Centers for Disease Control and Prevention's (CDC) initiative to eliminate the disease domestically by 2005, syphilis incidence has increased dramatically since 2000, especially among men who have sex with men (MSM) [5–10]. In 2002, 6862 cases of primary and secondary syphilis were reported nationally, representing a 12.4% increase over the previous year, and compared to the previous decade's nadir of 5979 cases in 2000 [10]. For instance, in California during the first half of 2003, 670 cases of primary and secondary syphilis were reported, a 400% increase from the same period in 1999, of which 79% were MSM and of those, 60% were HIV-positive by self-report, with most (59%) reporting anonymous sex partners (Samuel, Personal communication).

This resurgence of syphilis has been linked to increases in the number of anonymous sex partners, decreases in condom use, use of the Internet for meeting sex partners, and more widespread use of methamphetamine and sildenafil (Viagra; Pfizer Inc., New York, NY), among other drugs [11–15]. Moreover, the indirect contribution of highly active antiretroviral therapy (HAART) to higher syphilis transmission rates among those infected with HIV has been well-described [16].

Screening for syphilis in HIV-infected patients

Recognition of a sexually transmitted disease (STD) in an HIV-infected patient is a sentinel clinical event that should trigger the provider's exploration of underlying risk behaviors, the patient's interpersonal HIV disclosure capacity, and his or her appreciation of risks posed to others [13]. Sexual health assessments should be a routine part of care for patients with HIV [17•]. For the patient with multiple sex partners or with a partner who has multiple partners, screening for STDs such as syphilis, gonorrhea, and chlamydia should be done annually [18••]. Experts now also recommend screening patients at higher risk for syphilis every 3 to 6 months, depending on the level of risk; factors include multiple anonymous partners, concomitant recreational drug use, or frequenting of commercial sex venues or Internet sex partner sites [17•,18••,19–22]. Because serum antibody to *T. pallidum* is not protective, reinfection may occur if risk is ongoing.

Clinical Features of Syphilis in HIV-infected Patients

Syphilis is well-known for its protean presentations, reflecting systemic dissemination of the treponeme. Aside from more common mucocutaneous and systemic features in the primary and secondary stages of the disease, widespread involvement in early and late syphilis may result in ocular, otologic, neurologic, gastrointestinal, hepatic, renal, and osseus manifestations, albeit rarely.

Syphilis features by stage

Conventional staging of syphilis is unaltered by HIV coinfection. Symptoms may appear within several days of exposure (mean, 21 days; range, 14–90 days) [12,23]. In primary syphilis, one or more ulcers (chancres) develop at the site of exposure, usually on the genitals or anus. Patients may be unaware of these typically painless lesions, especially if located inside the vagina or anus. Regional nontender lymphadenopathy may develop. If the ulcer or ulcers become infected secondarily, painful lesions and/or adenopathy may be observed. The chancre then resolves, usually before secondary stage onset, with or without treatment.

In the secondary stage, symptoms typically include generalized or localized skin eruptions and mucosal lesions. They may be mild or florid and most commonly include a wide morphologic variety of rashes (ranging from macular, papular, pustular, papulosquamous, to annular) that may cover the palms and soles. Constitutional symptoms (*eg*, sore throat, low-grade fever, malaise, myalgias, arthralgias, generalized lymphadenopathy) also may be present. Less common symptoms and signs include mucous patches in the oropharynx, condylomata lata, or moist, wart-like papules occurring mostly in skin folds, and alopecia. The rash of secondary syphilis can mimic many dermatologic conditions, such as tinea versicolor, pityriasis rosea, scabies, fixed drug eruptions, and erythema multiforme; in HIV-infected patients receiving HAART, it has been misdiagnosed as an antiretroviral drug reaction.

In general, infectious syphilis refers to the primary and secondary stages because syphilitic chancres, mucous patches, and condylomata lata are highly infectious lesions. By exception, dry rashes typically are noninfectious. Like primary lesions, secondary symptoms and signs resolve without therapy; such resolution marks the beginning of the latent period of disease.

In latent syphilis, serologic evidence is found despite absence of symptoms or signs of the primary and secondary stages. Relapses of secondary syphilis symptoms and signs may occur early in the latent stage. Early latent syphilis is defined by the CDC as infection less than 12 months in duration, evidenced in the prior year by a negative serologic test, symptoms or signs of primary or secondary syphilis, or contact with a sex partner with early-stage syphilis [18••]. If there is no evidence to suggest the infection was acquired in the preceding 12 months by these criteria, then the duration of infection is unclear and is referred to as syphilis of unknown duration. In this case, even if the patient had a negative or four-fold lower nontreponemal serologic test result more than 12 months ago, it is impossible to determine the time of acquisition since the previous test if risk behaviors occurred throughout this time period.

Tertiary syphilis describes disease with late manifestations, encompassing cardiovascular features such as aortitis with aneurysm formation, late neurologic sequelae, and formation of gummas (indolent albeit destructive granulomatous lesions that may occur in any organ but chiefly involve skin, bone, and liver). Neurosyphilis is not a stage but rather a site of infection, where symptoms may manifest earlier or later in the course of infection.

Modified presentation in the HIV/*Treponema pallidum*–coinfected patient: redux of the "great imitator"

With minor exceptions, syphilis was not found to present or progress atypically in an important, large-scale, prospective trial of 101 HIV-infected patients that evaluated treatment outcomes in early-stage infection, as reported by Rolfs *et al*. [24••]. Numerous early case reports and more recent reviews have sought to characterize the extent to which HIV infection alters the clinical presentation of syphilis, with most minimizing its impact (Table 1) [25•,26,27,28•].

Seventy percent of HIV-infected patients in one study presented initially with multiple chancres rather than a single ulcer, compared to 34% of HIV-negative patients ($P < 0.05$) [24••]. Others have suggested primary lesions may be more severe and/or slow to resolve, although these data are less convincing. However, in a study of 253 patients with secondary syphilis, 25% of those with HIV presented with persistent genital ulcers, compared to only 14% of HIV-uninfected patients [28•]. Therefore,

Table 1. Atypical features of syphilis in HIV-infected patients reported in the medical literature

Stage	Sign, symptom, or other finding	Variation reported in HIV-infected patients	Primary studies
Primary*	Chancre (primary ulcer)	Multiple (instead of single) lesions	Rolfs *et al.* [24••], Rompalo *et al.* [28•]
Secondary†	Initial presentation	More likely to present initially with secondary syphilis manifestations	Hutchinson *et al.* [27]
	Primary genital lesions	More often persistent in presentation of secondary stage	Hutchinson *et al.* [27], Rompalo *et al.* [28•]
Any	Nontreponemal test results	Higher-titer results	Rolfs *et al.* [24••]
	Biologic false-positive syphilis tests	Increased frequency	Rompalo *et al.* [45], Yinnon *et al.* [54], Joyanes *et al.* [44]
	Serologic failure after treatment	Increased frequency despite lack of correlation with adverse clinical outcomes	Malone *et al.* [53], Yinnon *et al.* [54], Rolfs *et al.* [24••]
	Prozone phenomenon	Increased frequency	Jurado *et al.* [42]
	Jarisch-Herxheimer reaction	Increased frequency	Rolfs *et al.* [24••]
Neurologic site involvement	Normalization of CSF values after treatment for neurosyphilis	Delayed	Marra *et al.* [38]

*Significant differences have not been shown in duration or other features of primary syphilis lesions in HIV-infected individuals, compared with HIV-uninfected individuals, nonwithstanding case reports.
†Significant differences have not been demonstrated in other secondary syphilis manifestations in HIV-infected, compared with HIV-uninfected, individuals.
CSF—cerebrospinal fluid.

presentation involving a combination of primary and secondary features should not cause one to doubt syphilis as the underlying diagnosis. Furthermore, in evaluating possible secondary syphilis, careful genital and rectal examinations remain worthwhile for identification of resolving primary lesions.

Neurologic Involvement in HIV/ *Treponema pallidum*–coinfected Patients

Central nervous system (CNS) invasion in syphilis may occur at any time in the course of infection and has been shown to occur early [29]. Neurologic involvement, including definitive neurosyphilis, may be seen during primary, secondary, and early latent stages of infection, as well as during late stages [30].

Ophthalmologic and otologic sequelae

Clinicians should be aware of ocular and otologic sequelae observed in HIV/*T. pallidum*–coinfected patients. Ocular manifestations include uveitis [31], chorioretinitis [32], and retrobulbar neuritis [33]. Among these, uveitis is the most common and was found in 10% of patients with a positive cerebrospinal fluid (CSF) treponemal test in San Francisco between 1985 and 1992 [34]. In rare cases, retinal detachment and blindness may occur. Otologic involvement is infrequent and may present with asymmetric hearing loss, tinnitus, or vestibular disturbances. Whether incidence of these manifestations is increased in HIV-infected patients is uncertain, and reliable clinical predictors have not been identified.

Neurosyphilis

In the normal host, immunologic mechanisms are thought to modulate control of CNS infection, even in the absence of definitive therapy [35]. Given compromised immunity in HIV infection, concern about neurologic involvement is heightened. Early case reports queried a more aggressive course [36,37], despite comparable observations having been described in the pre-HIV era [30]. Numerous investigators have found no differences in *T. pallidum* detection by polymerase chain reaction (PCR) in HIV-infected versus HIV-uninfected patients [24••,29, 38]. However, one recent study again has raised the question of whether neurologic involvement is more common in HIV-infected persons [38]. The precise extent and significance of such involvement, reflected by laboratory or clinical criteria, remain incompletely characterized. Moreover, the modulation of host immunosuppression by HAART in recent years has further challenged this understanding.

In early neurosyphilis, which may be asymptomatic and occur soon after infection, the blood vessels and meninges are preferentially affected. Early disease includes syphilis meningitis and meningovascular syphilis, with symptoms including headache, cranial nerve and/or ocular involvement, and stroke. Late neurosyphilis involves the meninges and the parenchyma of the brain or spinal cord. It typically occurs years after infection and entails the more dramatic but rare presentations of general paresis, a chronic, insidious meningoencephalitis, and tabes dorsalis, posterior column involvement of the spinal cord causing sensory ataxia, as well as bowel and bladder dysfunction.

Epidemiologic data suggest symptomatic neurosyphilis is not increased in the setting of HIV infection. In a retrospective review in San Francisco from 1985 to 1992, two to nine cases of symptomatic neurosyphilis were identified per year, with no increase during the study period despite the highest rates of infectious syphilis in the United States in the early 1980s and a dramatic increase in its AIDS cases (from 116 to more than 3000) in the decade before 1992 [34]. More recent surveillance has confirmed a low incidence of laboratory-defined neurosyphilis, found in only 2.3% (14/602) of syphilis cases (all stages) in San Francisco in 2002 (Wong, Personal communication). Nonetheless, given residual uncertainty about the frequency and significance of neurologic involvement in HIV/*T. pallidum*–coinfected patients and the need for procaine or aqueous crystalline penicillin G (ACPG) to treat this site of infection, careful clinical neurologic evaluation of all patients with syphilis is critical, with special attention to cranial nerve deficits. In addition, neurosyphilis and ocular syphilis always must be considered in any HIV-infected patient with neurologic symptoms and visual changes.

Diagnosis of Syphilis

Despite subtle differences in clinical presentation, syphilis is diagnosed in HIV-infected patients according to conventional criteria. An overview of syphilis diagnosis and management in HIV-infected patients is provided in Figure 1.

Use of serologic tests

Nontreponemal assays that use cardiolipin-, lecithin-, and cholesterol-containing antigen to measure antilipoidal antibodies, such as the rapid plasma reagin (RPR) card or venereal disease research laboratory (VDRL) tests, often are used initially to diagnose syphilis. Treponemal assays (*T. pallidum* particle agglutination [TP-PA], fluorescent treponemal antibody absorbent [FTA-Abs]) are used to confirm the results of nontreponemal tests in a two-step, reflex process. In general, interpretation of these tests is unchanged by HIV infection. Nonetheless, serologic testing should not be relied on exclusively to identify syphilis infection. Evidence for the diagnosis should be sought from all available sources, such as patient history, sex partner history, findings from clinical examination, previous serologic results, and if possible, direct laboratory examination, or if necessary, biopsy of suspicious lesions.

Misidentification of infected persons

The sensitivity of serologic tests for syphilis increases with duration of infection and ranges from approximately 75% in the primary stage to virtually 100% in the secondary stage [39]. In general, sensitivity of nontreponemal and treponemal tests in HIV-infected patients is as high as that in HIV-negative patients, and these test results should be interpreted in the usual manner. Because the sensitivity of nontreponemal and treponemal tests is lower in the primary stage, a negative serologic test result in an HIV-infected patient with a genital lesion cannot exclude primary syphilis. Although limited case reports in the early 1990s raised concerns about falsely negative serologic test results in HIV-infected patients with secondary syphilis [40,41], no studies have been reported in the past decade to quantify these observations.

The prozone phenomenon may cause a false-negative nontreponemal test result, usually during secondary syphilis, when a high concentration of treponemal antigen does not permit detectable antigen-antibody complex formation. This may be overcome by diluting the specimen, which should be specifically requested by the clinician when a case is highly suspicious despite nonreactive nontreponemal test results. Although limited reports have suggested this may occur more often in HIV-infected patients, definitive evidence is lacking [42].

Of greater concern is the lack of improved diagnostic tests for primary syphilis, because a negative serologic test result cannot rule out syphilis. Most providers do not have access to dark-field microscopy. Although a multiplex PCR test for GUD has been developed and has excellent sensitivity (approximately 95%) for syphilis, herpes simplex, and chancroid, there are no plans to market this test in the United States [43].

Because serologic diagnosis of syphilis may be complicated in the HIV-infected patient, direct laboratory examination of suspicious lesions should be considered. If such examination of presenting lesions is not readily available, if serologic testing reveals equivocal or negative results, or if such results are unavailable and the index of suspicion is high, presumptively treatment is reasonable, with close follow-up and repeat serologic testing after 1 to 2 weeks to detect a delayed antibody response. When evidence points to syphilis in the face of nonreactive serologic testing, further evaluation is required.

Misidentification of uninfected persons

The specificity of nontreponemal tests also may be altered by HIV. More often in HIV infection, nonspecific polyclonal B-cell activation may result in biologic false-positive or higher nontreponemal test titers than those observed in HIV-uninfected patients [44,45]. In general, positive nontreponemal test results, particularly with titers greater than 1:8, should be interpreted as indicating active infection, with interval testing to assess delayed seroreactivity of the confirmatory test. The influence of HIV on the specificity of nontreponemal tests also complicates the management of fluctuating titers seen in sexually active HIV-infected patients previously treated for syphilis. In such patients, it is impossible to determine whether a rising titer results from a new infection, reaction from an inadequately treated infection, or is caused by HIV infection itself. Management depends on assessment of risk behaviors and likelihood of treatment failure.

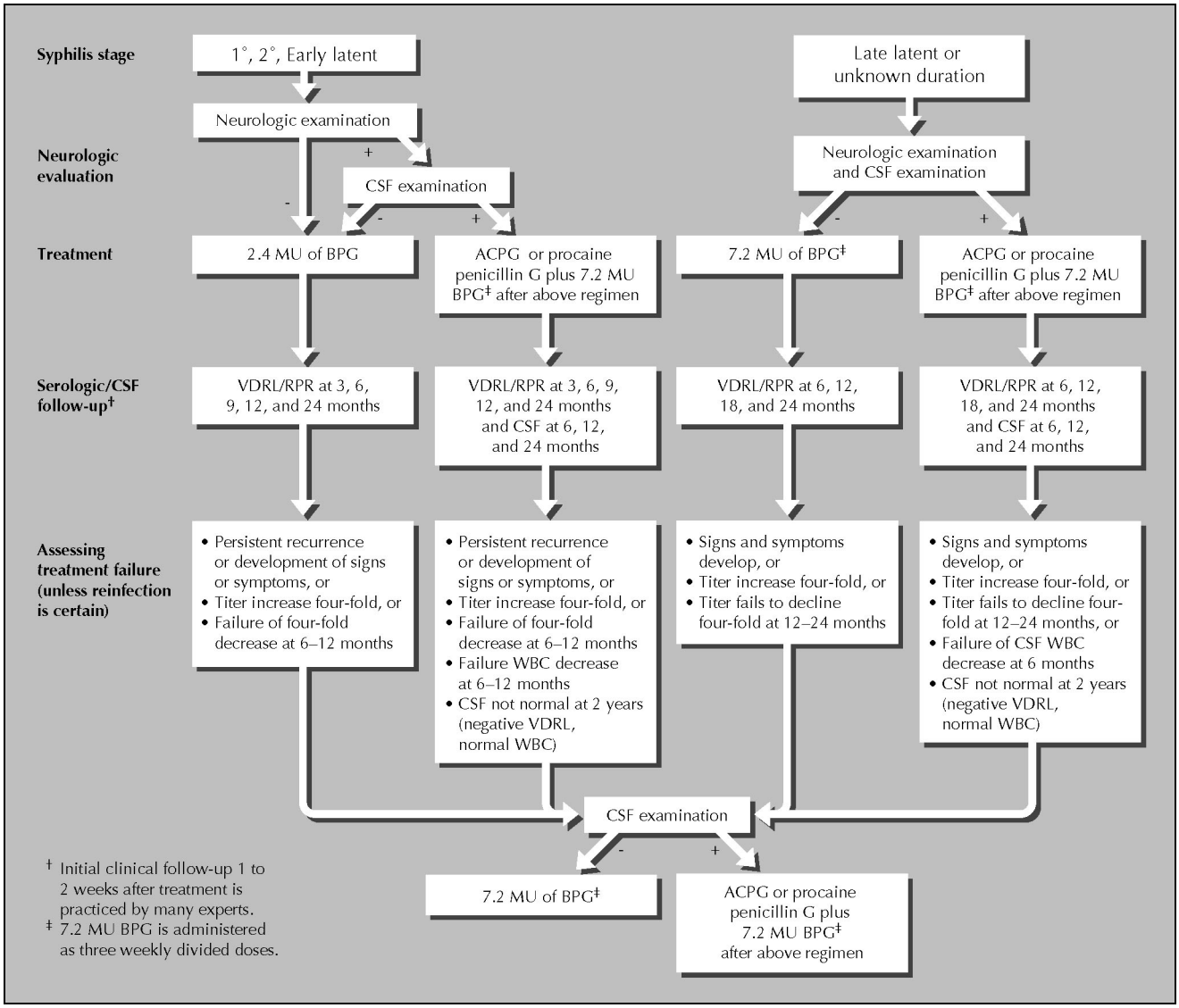

Figure 1. Algorithm for management of syphilis in HIV-infected patients. ACPG—aqueous crystalline penicillin G; BPG—benzathine penicillin G; CSF—cerebrospinal fluid; RPR— rapid plasma reagin; VDRL—venereal disease research laboratory; WBC—white blood cell. (*Adapted from* Cohen *et al.* [59].)

Diagnosis of neurosyphilis

In HIV-infected patients, neurosyphilis should be considered in the differential diagnosis of any disease presenting with neurologic findings. In these cases, basic serologic testing and appropriate examination of the CNS for neurosyphilis is an essential part of the work-up (Fig. 2). Although *T. pallidum* can be isolated from the CSF in a proportion of asymptomatic HIV-infected patients with early syphilis, the clinical and prognostic significance of such detection remains unclear. Furthermore, PCR testing of CSF to detect *T. pallidum* has been insufficiently sensitive to aid the diagnosis of neurosyphilis [24••]. Despite extensive study and varying recommendations, experts continue to disagree about the defined role of CSF analysis in the routine management of syphilis in HIV-infected patients.

The diagnosis of neurosyphilis is based on one or more positive CSF findings. These include a reactive VDRL assay or—when nonreactive—pleocytosis (> 10–20 white blood cells [WBCs] per mm^3) with or without elevated protein concentration (> 45 mg/dL) in the absence of other known causes of these abnormalities. However, fully attributing elevated CSF WBC or protein levels to the effect of syphilis alone can be problematic because either may be elevated in the natural history of HIV infection [46]. Although CSF FTA-Abs lacks specificity in the CSF, a negative result has a high negative predictive value and is recommended by some experts to exclude neurosyphilis in CSF VDRL-negative cases in which minimal abnormalities in WBCs and/or protein raise concern.

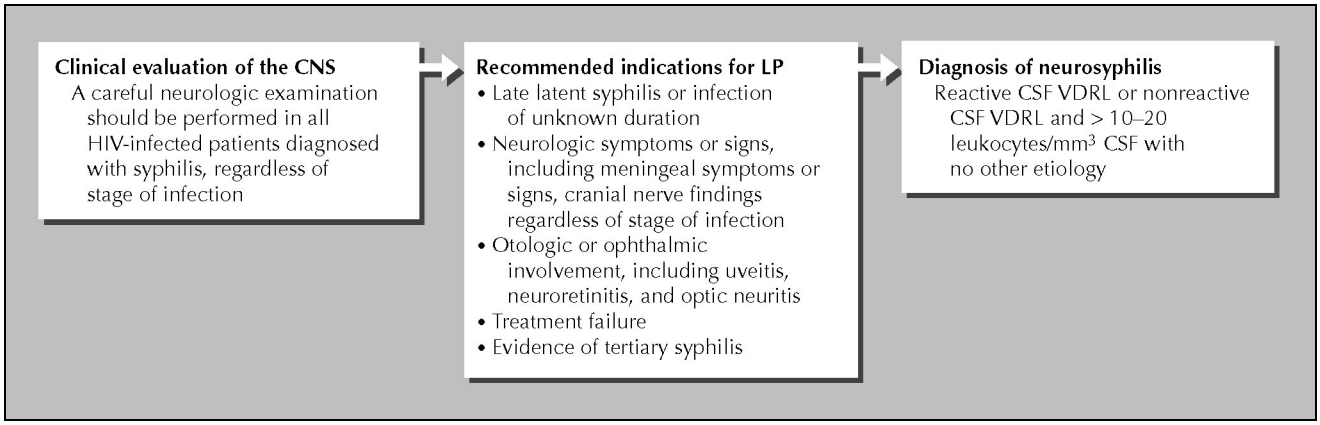

Figure 2. Central nervous system evaluation in HIV-infected patients with syphilis. CNS—central nervous system; CSF—cerebrospinal fluid; LP—lumbar puncture; VDRL—venereal disease research laboratory.

Published recommendations for performance of lumbar puncture (LP) seek to identify those at greatest risk for neurologic sequelae. Rolfs *et al.* [24••] described no benefit associated with enhanced treatment for neurosyphilis in early-stage infection. Yet, because of theoretical concern about neurologic complications in HIV-infected patients who have been unable to clear this sequestered site of infection after 1 year, the CDC recommends performing LP in all HIV-infected patients with late latent syphilis or infection of unknown duration [18••]. Other criteria for performance of LP, such as neurologic, ophthalmic, or otologic symptoms or signs, tertiary syphilis, or treatment failure, hold regardless of HIV infection status.

Recently, Marra *et al.* [38] identified a nearly six-fold increased risk for laboratory-defined neurosyphilis in HIV-infected patients with primary, secondary, or latent syphilis and a serum titer ≥ 1:32, as well as a more than three-fold risk in these patients with a CD4+ T-cell (CD4) count less than 350 cells/mm^3. In patients with both of these findings, laboratory-defined neurosyphilis was greater than 18 times more likely [38]. However, longitudinal data were not provided comparing the outcome of patients treated with intravenous (IV) penicillin to that of patients with early latent syphilis and a titer ≥ 1:32 treated with intramuscular (IM) benzathine penicillin G (BPG), as is currently recommended by CDC.

Such data have prompted experts to propose CSF evaluation based on CD4 count and nontreponemal test titer. For instance, Kassutto and Sax [47] suggest considering LP in HIV-infected patients with nontreponemal titer more than 1:32 independent of syphilis stage or CD4 count, as well as in patients with early-stage infection and CD4 count less than 350 cells/mm^3, regardless of titer. For patients with CD4 count ≥ 350 and RPR ≤1:32, they do not recommend LP [47].

Because of extant complexities, clinical judgment is required in deciding to perform LP and in making the diagnosis of neurosyphilis. Furthermore, the clinical benefit of treating laboratory-defined neurosyphilis during early-stage infection has not been fully established, in the wake of the study by Rolfs *et al.* [24••] that supported no such benefit, at least at 1 year of follow-up. However, emerging data underscore the need to consider neurosyphilis in patients with high serum syphilis titers and more advanced HIV infection, and to ensure close follow-up of such patients with early syphilis treated with IM BPG in the absence of a CSF examination.

Treatment of Syphilis

General treatment considerations

Long-acting, injectable BPG remains the treatment of choice for all stages of infection. In early syphilis (primary, secondary, and early latent), a single IM injection of BPG (2.4 MU) should be administered. In late latent syphilis or infection of unknown duration, 7.2 MU of BPG in three weekly divided doses should be administered, after the patient has had an LP for examination of the CSF to rule out neurosyphilis [18••] (Table 2). In such a patient who is sexually active, it is impossible to rule out recent infection with the potential for symptom development and further transmission of infection; therefore, examination of CSF, if indicated, must be timed to avoid delay in treatment.

Because of the current epidemic among MSM, any men with same-sex partners presenting with new genital ulcers, rashes, or wart-like lesions should be empirically treated for syphilis at that visit, even before serologic test results are available. Most public health laws require treatment of suspected cases of communicable diseases before waiting for confirmatory test results. In addition, because titers can increase rapidly in early infection, clinicians must obtain a serologic test on the day of treatment, because this titer will be followed to monitor treatment adequacy. Even if a titer was done 2 weeks before this visit, it should be repeated on the day of treatment.

In HIV-negative nonpregnant adults, particularly those with an allergy to penicillin, doxycycline and tetracycline are

Table 2. Treatment of syphilis in HIV-infected patients*

Primary, secondary, and early latent infection
Benzathine penicillin G, 2.4 MU IM in a single dose--
Additional considerations
Alternative regimens (*eg*, tetracyclines, azalides) not well-studied in HIV infection; careful follow-up recommended.
Follow-up includes clinical evaluation at 1 to 2 weeks followed by clinical and serologic evaluation at 3, 6, 9, 12, and 24 months after treatment
Late latent infection and infection of unknown duration
Diagnostic recommendation
LP for CSF evaluation before treatment
Treatment
If CSF values are normal, administer benzathine penicillin G, 7.2 MU divided in three weekly IM doses.
Otherwise, treat for neurosyphilis, as below.
Additional considerations
Alternative regimens (*eg*, tetracyclines) are not well-studied in HIV infection; careful follow-up is essential when they are administered to treat late infection
Follow-up includes clinical and serologic evaluation at 6, 12, 18, and 24 months after treatment
Neurosyphilis (including ophthalmologic or ocular involvement)
Aqueous crystalline penicillin G, 18–24 MU per day (3–4 MU every 4 hours) for 10–14 days
Additional considerations
In compliant patients, an acceptable alternative is procaine penicillin 2.4 MU IM once daily plus probenecid 500 mg orally four times per day, both for 10–14 days; another, less studied alternative is IV ceftriaxone 2 g daily for 14 days
Most experts recommend benzathine penicillin G, 7.2 MU, divided in three weekly IM doses, after completion of the above
Penicillin-allergic and pregnant patients
Alternatives to penicillin (*eg*, tetracyclines, azalides) are not well-studied in HIV infection. Tetracyclines are contraindicated in pregnancy. Probenecid should not be administered to patients with allergy to sulfa-based medications. Skin testing and/or desensitization to facilitate therapy with penicillin is recommended in pregnant patients and for treatment of latent syphilis and neurosyphilis in other patients with HIV infection.

*Recommended by the US Centers for Disease Control and Prevention; other recommendations as indicated.
CSF—cerebrospinal fluid; IM—intramuscularly; IV—intravenously; LP—lumbar puncture.

alternatives for treating early syphilis and have been used for decades with anecdotal success. Because dosing over 14 days is required, efficacy is compromised by potential nonadherence in addition to pharmacologic properties diminishing their activity compared to BPG. These agents have not been studied thoroughly in HIV-infected patients, and thus, are not considered standard therapy. Their use requires caution, and close follow-up is needed to assess clinical and serologic response.

Azithromycin, an azalide with high tissue penetration and a long half-life [48], garners continued interest for the treatment of early syphilis, but the long-term efficacy of this antimicrobial has not been clearly established. Some argue for the practical value of single-dose oral therapy because injectable BPG is a barrier to treatment in some patients. In addition, use of azithromycin as patient-delivered partner therapy holds promise as a tool for community-level control of the disease. In a study of 74 (96% HIV-negative) patients, azithromycin was administered as a single 2-g dose or two 2-g doses divided by 1 week, and researchers showed efficacy comparable to BPG. Serologic response was seen in 86% of patients in the penicillin group at 12 months, compared to 94% and 83% response in the azithromycin groups, respectively [49]. However, azithromycin has not been studied thoroughly in HIV-infected patients or for late syphilis, and thus, it is not considered standard therapy. Its use requires caution, with close follow-up to assess clinical and serologic response.

The Jarisch-Herxheimer reaction, an acute systemic response possibly related to release of treponemal antigen and endotoxin after treatment, has been found to occur more often in HIV-infected patients. Rolfs *et al.* [24••] observed the reaction in 22% of HIV-infected patients, compared to only 12% of patients without HIV infection ($P = 0.02$). Flu-like symptoms may include fever, malaise, arthralgias, and worsening of rash and mucocutaneous lesions. Thus, advise patients to anticipate such symptoms in order to avoid their confusion with adverse drug reactions.

Treatment of neurosyphilis

When syphilis involves the CNS, BPG is considered inadequate therapy because it does not cross the blood-brain barrier [50]. The established treatment remains IV ACPG, 18 to 24 MU per day in divided doses for 10 to 14 days. A regimen of daily IM procaine penicillin G, in combination with oral probenecid, is an acceptable substitute. Most experts recommend the addition of 7.2 MU of BPG in three weekly divided doses as follow-up to these regimens [18••], although the benefit of this practice has not been evaluated in a prospective manner.

Neither the tetracyclines nor azithromycin has been studied adequately in HIV-infected patients to support the

recommendation of either for treatment of neurosyphilis. The only alternative that has been studied is ceftriaxone 2 g IM for 14 days. The small sample size of this study precludes its recommendation as standard therapy [51], although the drug can be considered in special circumstances in which neither ACPG nor procaine penicillin is feasible. For the penicillin-allergic HIV-infected patient with neurosyphilis, and when concern for cephalosporin allergy also exists, desensitization to penicillin is the only option [18••]. Evaluation of penicillin allergy with preliminary skin testing may obviate the need for desensitization.

Although Rolfs *et al*. [24••] did not observe a benefit treating early syphilis with BPG plus amoxicillin/probenecid (intended to achieve substantially greater CNS treponemicidal activity compared to BPG alone), some experts remain concerned about the significance of CNS invasion in early-stage disease. Investigation of alternative and/or prolonged therapy for early-stage syphilis in HIV infection continues.

Syphilis Follow-up

General follow-up recommendations

Careful and enhanced follow-up of the HIV/*T. pallidum*–coinfected patient is critical (Fig. 1). Although general follow-up evaluations for syphilis should occur at 6 and 12 months, patients coinfected with HIV should be reexamined 1 to 2 weeks after treatment, then evaluated clinically and serologically at 3, 6, 9, 12, and 24 months in early-stage infection and at 6, 12, 18, and 24 months in late-stage infection.

In HIV-infected patients with early syphilis, the definition of successful serologic response to treatment is a four-fold (or two-dilutional) decrease in the nontreponemal test titer over the 6- to 12-month period after treatment. Such a decrease in titer should be expected 12 to 24 months after therapy in late latent syphilis or disease of unknown duration. Serum VDRL and RPR titers are not interchangeable and should not be compared. A persistent, low-level positive nontreponemal titer (usually ≤ 1:8), reflecting a "serofast" state, has been found to occur more frequently in HIV/*T. pallidum*–coinfected patients [24••].

For patients diagnosed with neurosyphilis with CSF pleocytosis initially present, follow-up should include CSF examination until the pleocytosis resolves, at 6, 12, and 24 months as required. In these patients, if cell count is not normal after 6 months, or if all CSF parameters are not normal after 2 years, retreatment should be considered [18••]. Recent data suggest CSF VDRL, WBCs, and protein in particular may normalize more slowly in HIV-infected patients after neurosyphilis treatment, although it remains unclear whether this reflects treatment failure [52].

Treatment failure

Evidence suggests that treatment failure, as defined by serologic response, is slightly more common in the syphilis patient coinfected with HIV, although clinical significance is unclear and correlation with adverse clinical outcomes has not been demonstrated [24••,53,54]. Thus, the clinical and serologic response must be monitored in all patients treated for syphilis.

When the serum syphilis titer does not decrease as expected, treatment failure is a possibility, and these patients should undergo LP for CSF examination and be retreated with 7.2 MU of BPG in three weekly divided doses if the CSF parameters are within normal limits. Subsequent follow-up should involve clinical and serologic evaluation every 6 to 12 months. If titer fails to decrease further or does not revert to normal after treatment, such "serofast" patients should be followed annually for further evidence of clinical or serologic relapse [18••]. However, in HIV-infected patients, persistent "serofast" titers can be higher and do not appear to correlate with active infection. Thus, the CDC recommends no further therapy or CSF examination in those treatment failure cases if the titer remains stable. Certainly, ongoing risk for re-exposure complicates these assessments.

Fluctuating titers in previously treated, sexually active, HIV-infected patients also have been reported anecdotally. Any documented four-fold increase in titer causes concern for active infection, from reactivation of previously treated infection or reinfection. In this situation, the most conservative approach is to presume treatment failure and proceed with CSF examination, followed by retreatment with 7.2 MU of BPG in three weekly divided doses if CSF parameters are normal. If a four-fold increase in titer is observed and, based on sexual history, risk of reinfection is thought to be low, the titer should be repeated in 2 weeks to see if the increase is sustained. If sustained, one must assume active infection is possible from reactivation or reinfection and proceed with LP and retreatment as noted earlier.

Treatment of Sex Partners

The sex partners of patients with syphilis should be treated presumptively with BPG (2.4 MU) or an alternative such as doxycycline or azithromycin if exposed within 90 days of the diagnosis of the partner. Those exposed more than 90 days before diagnosis should be tested and treated presumptively if results of serologic tests are unavailable or if follow-up is uncertain. Other sex partners should be evaluated serologically and clinically, based on risk defined by stage of disease of the diagnosed partner [18••]. All patients treated for syphilis should be offered testing for HIV and other STDs.

Public health departments assist patients with infectious syphilis in facilitating partner treatment because most partners are unaware they have been exposed. Because of syphilis' incubation period, if partners can be identified and treated in a timely fashion, further spread of this infection can be reduced dramatically. Therefore, providers need

to counsel their patients about the availability of such services, as appropriate.

Secondary HIV Transmission

In HIV-infected patients, coinfection with syphilis may, in turn, enhance the risk for secondary HIV transmission to uninfected partners [1]. Molecular pathogenetic mechanisms have been proposed to explain the role of *T. pallidum* in facilitating HIV transmission, one involving upregulation of HIV gene expression, such as that of the CCR5 coreceptor for HIV entry [55,56]. In a study of 35 MSM with HIV infection, CD4 cell counts declined and previously detectable HIV RNA increased in 57% of those with incident syphilis infection ($P = 0.06$) [57]. Thus, in HIV-infected patients with increases in plasma RNA, syphilis should be a consideration, in addition to other coinfections, virologic drug failure, and nonadherence. Such biologic mechanisms, in combination with behavioral factors, render imperative the provision of HIV/STD risk reduction counseling to patients coinfected with HIV and syphilis.

Providers' Role in Syphilis Control

In recent years, syphilis has been diagnosed primarily in HIV care and private practice settings. For example, in California, only 10% of cases in 2002 were identified through STD clinics [58]. This backdrop, in conjunction with the acute increase in syphilis incidence among persons with HIV infection—MSM in particular—positions providers to take a lead in the control of syphilis spread. Practical strategies include routine risk assessment and sexual history taking, serologic screening every 3 to 6 months based on sexual risk factors, heightened awareness of the variable presentation of syphilis in HIV-infected patients, active sex partner management, client-centered risk reduction counseling, and timely reporting of incident cases as well as follow-up serologies. In addition, providers should be aware of state-specific regulations concerning syphilis reporting, treatment, and partner notification.

Conclusions

With increasing rates of syphilis among persons with HIV infection, further expansion of our knowledge of the clinical management of syphilis in HIV/*T. pallidum*–coinfected patients is critical. New and improved diagnostic alternatives are necessary. Refined clinical and serologic predictors of long-term and neurologic outcomes in coinfected patients will help clarify the role of CNS evaluation and clinical follow-up. HIV-infected patients should be enrolled in studies evaluating alternative treatment regimens. Working closely with local providers, public health authorities must employ the latest of strategies aimed to control the spread of new infections in high-risk populations. Most important, innovative and focused prevention efforts are needed to stem the untimely re-emergence of syphilis and, in turn, its stealthy sequelae.

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