Syphilis and HIV Infection: An Update

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The striking increase in the prevalence of concordant human immunodeficiency virus (HIV) infection and syphilis observed by clinicians and public health officers over the past decade has renewed interest in the subject. Although the effect of HIV infection on the natural history of syphilis has been known for a long time, it was not until recently that several studies documented that syphilis may also impact the course of HIV infection. Despite an improved understanding of the interaction of these 2 conditions, many controversies still exist. In this article, we focus on the most recent literature describing the epidemiology, clinical manifestations, and treatment of syphilis in the context of HIV infection.

The interaction between syphilis and HIV infection is complex and remains incompletely understood, despite there being >2 decades of clinical experience with coinfected patients. Since its last review in this journal [1], new data have emerged increasing our understanding of the interaction between HIV infection and syphilis that apply to both the heterosexual population and men who have sex with men (MSM).

EPIDEMIOLOGY

After steady decreases for >1 decade, rates of syphilis in the United States reached their lowest point during 2000, when the rate of primary and secondary syphilis was 2.1 cases per 100,000 persons [2]. By 2005, the rate of primary and secondary syphilis increased to 3.0 cases per 100,000 persons, representing an increase from 5976 to 8724 cases, of which 86% occurred in men. This increase in the rate ratio of male to female patients (from 1.2 in 1996 to 5.7 in 2005) was a reflection of the disproportionate burden of disease among MSM, who accounted for ~65% of all persons with primary and secondary syphilis [2].

Large cities with well-established populations of MSM have been the most affected by this shift in the epidemic. In California, there was a >700% increase in primary and secondary syphilis cases reported between 1999 and 2005. Among those cases, 80% involved MSM. Given that there are well-established epidemics of HIV infection among MSM from large metropolitan areas, an increasing number of cases of concurrent syphilis and HIV infection were being reported. In California, ~60% of MSM with syphilis are HIV infected, and it is estimated that, in major cities, 20%–50% of MSM with syphilis have concurrent HIV infection [2–4].

Reasons for this rapid increase in the rate of syphilis among HIV-infected MSM are complex. The increase in the rate of syphilis and other sexually transmitted diseases (STDs) among MSM suggests a decrease in safer sex practices [5]. In this regard, the success of HAART, the use of the Internet to meet sex partners, the increased frequency of serosorting (i.e., finding sex partners with the same HIV serostatus), and the increase in recreational drug use, both illicit (e.g., crystal methamphetamine) and prescribed (e.g., sildenafil citrate), have all likely contributed to increases in the rate of syphilis [6–8]. In addition, the idea that oral sex is "safer" sex and rarely associated with HIV transmission may explain the role of oral sex in syphilis transmission [9–11].

Given that primary syphilis facilitates both the transmission and the acquisition of HIV infection [12–15], expansion of the HIV epidemic within the MSM population is a concern. However, to date, there is no clear evidence of increased spread of HIV infection [16]. Actually, the annual incidence of HIV infection among MSM at the San Francisco, California, municipal STD clinic decreased between 1999 and 2001 from to 5.4 cases per 100 person-years to 2.5 cases per 100 person-years, despite there being dramatic increases in the rates of primary and secondary syphilis during the same period. Although there are no data on the effect of syphilis on the incidence of HIV infection at a national level, studies from Los Angeles, California, and Seattle–King County, Washington, coincide with San Fran-

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cisco's experience [17–19]. Although the reasons for that discordance in trends are unknown, possible mechanisms include the high frequency of serosorting and the common practice of oral sex, which facilitates the spread of syphilis but not HIV infection [9, 16, 17]. Finally, a resurgence in the rate of syphilis has also been observed in heterosexual populations, potentially presaging the further spread of the HIV epidemic into other groups.

CLINICAL PRESENTATION

Despite minor differences, syphilis presents similarly in HIV-infected and HIV-uninfected patients. In primary syphilis, HIV-infected patients may present with >1 chancre (up to 70% of patients) and with larger and deeper lesions [20, 21]. Approximately one-fourth of HIV-infected patients present with concomitant lesions of both primary and secondary stages of syphilis at the time of diagnosis [20, 22]. Although atypical and aggressive presentations of syphilis occur more frequently among HIV-infected patients, these represent a very small minority of the cases [21]. Rather than "unique" presentations of syphilis, these atypical presentations likely represent an increased occurrence of traditionally uncommon manifestations.

The effect of syphilis on the HIV load and CD4 cell count has been recently documented in several studies (table 1) [23–28]. Taken together, these studies suggest that syphilis, like many other acute infections, causes transient increases in the viral load and decreases in the CD4 cell count that resolve after the infection is treated [23–25, 28]. It is possible that these transient increases in viral load contribute to the increased risk of HIV transmission among patients with concordant HIV infection and syphilis [15, 29]. How these transient changes affect the overall course of the HIV disease or the risk for syphilis transmission remains unknown. Importantly, however, clinicians should be aware that syphilis may account for otherwise unexplained decreases in CD4 cell counts or increases in the plasma viral load in HIV-infected patients. Syphilis testing might be indicated in such clinical scenarios.

NEUROSYPHILIS

Approximately one-third of patients with early syphilis have invasion of treponemes in the CSF, regardless of their HIV status [21, 30]. However, in contrast to HIV-uninfected patients, most of the new cases of clinical neurosyphilis in HIV-infected individuals are identified at the initial presentation (early), leading experts to believe that HIV infection may be associated with an increased risk of development of neurological complications [31]. Furthermore, a correlation between abnormal CSF findings suggestive of neurosyphilis and advanced HIV disease has been recently reported [32]. Therefore, it is possible that the apparent increased rate of early neurosyphilis among HIV-infected patients depends on the inability to control the CNS infection after invasion, rather than an increased actual rate of CNS invasion. However, it is possible that the apparent increased rates of neurosyphilis among HIV-infected patients reflect a referral bias of patients with higher rates of baseline abnormalities, traditionally used to define neurosyphilis in HIV-uninfected individuals (see below).

Regardless of the host's ability to control the infection and/or the immune status of the patient, CSF abnormalities can be seen during the early period of treponemal invasion of the CNS and may persist even after appropriate treatment. Higher cell counts, higher protein levels, and lower glucose levels in the CSF are frequently reported in HIV-infected patients with syphilis, but the clinical and prognostic significance of such abnormalities remains unknown [32, 33]. In a prospective, randomized trial that assessed the impact of treating laboratory-defined neurosyphilis in HIV-infected patients, Rolfs et al. [30] found no difference in clinical outcome at 1-year follow-up. More recently, in a prospective cohort of 59 patients with neurosyphilis (46 of whom had concurrent HIV infection), Marra et al. [34] showed that HIV-infected patients with CD4 cell counts $\leq$200 cells/μL were 3.7 times less likely to normalize CSF–Venereal Disease Research Laboratory (VDRL) test results than were those with CD4 cell counts >200 cells/μL, suggesting, as previously discussed, that HIV-associated immunedysregulation may account for the impaired clearance of organisms from the CNS. Although it remains unknown whether the lack of normalization of CNS-VDRL results among HIV-infected patients reflects treatment failure, this study raised concerns regarding the adequacy of the current recommended treatment for neurosyphilis in this population [34].

Deciding who should undergo CSF examination is one of the most controversial issues in the management of coinfected patients. Although case reports about progression to neurosyphilis (despite administration of appropriate therapy for early syphilis) among HIV-infected patients led some clinicians to recommend that all patients with concurrent conditions should undergo CSF examination, it seems now that performing lumbar punctures in all such patients is unnecessary [34–37]. On the basis of limited data, the Centers for Disease Control and Prevention and most experts agree that CSF examination must be performed for HIV-infected individuals who receive a diagnosis of late latent syphilis, syphilis of unknown duration, neurologic signs or symptoms, or suspected treatment failure [38]. However, which other patients should undergo CSF evaluation is unknown.

Two recent studies found a significant association between serum rapid plasma reagin (RPR) titers of $\geq$1:32 and laboratory-defined neurosyphilis [32, 39]. In one of these studies, CD4 cell counts <350 cells/μL were also associated with laboratory markers of neurosyphilis, and the risk of abnormal CSF laboratory study

Table 1. Effect of syphilis on CD4 cell count and HIV load.

Study	Level before syphilis	Level during syphilis	Level after syphilis treatment	Change in level		Percentage of patients receiving ART
				From before to during syphilis	From during to after syphilis	
Sadiq et al. [23] (n = 63)[a]						43
CD4 cell count, cells/μL	485	410	475	−75[b]	+65	
HIV load, $\log_{10}$ copies/mL	3.74	4.22	4.24	+0.48	+0.02	
Kofoed et al. [24] (n = 38)						87
CD4 cell count, cells/μL	547	485	580	−58	+66	
HIV load, $\log_{10}$ copies/mL	1.28	1.30	1.28	+0.035	−0.26[c]	
Buchacz et al. [28] (n = 52)						58
CD4 cell count, cells/μL	NA	NA	NA	−62[c]	+33	
HIV load, $\log_{10}$ copies/mL	NA	NA	NA	0.21[c]	−0.10	
Manfredi et al. [27] (n = 36)						86
CD4 cell count, cells/μL	573	589	573	+16	−16	
HIV load, $\log_{10}$ copies/mL	3.3	3.2	3.5	−0.1	+0.3	
Palacios et al. [26] (n = 118)						51
CD4 cell count, cells/μL	590	496/509	597	−94[c]	+88[c]	
HIV load, $\log_{10}$ copies/mL	NA	NA	NA	+1.03/+1.46[c,d]	NA	

NOTE. ART, antiretroviral therapy; NA, not available/not provided.

[a] Only the median values are included in the table.
[b] Statistically significant only for the subgroup of patients with primary and secondary syphilis.
[c] Statistically significant.
[d] Data are the change for patients with detectable HIV load at baseline/change for patients with undetectable HIV load at baseline.

findings was significantly higher when both risk factors (i.e., serum RPR titer ⩾1:32 and CD4 cell count <350 cells/μL) were present in the same patient [32]. Those data have prompted some experts to recommend CSF examinations for HIV-infected patients with a nontreponemal serum titer ⩾1:32, regardless of the syphilis stage, or for those with early-stage infection and a CD4 cell count <350 cells/μL, regardless of titer [32, 40]. However, these studies do not provide longitudinal data to compare the effectiveness of neurosyphilis treatment with that of intramuscular benzathine penicillin G (2.4 million U) for patients with early syphilis and a titer ⩾1:32.

Given that thousands of patients with early syphilis have been treated with benzathine penicillin G without evident neurologic complications (even among patients with high RPR titers and low CD4 cell counts), the benefit of treating a laboratory finding of unknown prognostic significance remains unclear [31]. It is not our practice to recommend CSF examinations for HIV-infected patients who present with primary, secondary, or early latent syphilis and a lack of neurologic, visual, or auditory signs or symptoms, regardless of the RPR titer or CD4 cell count. Current indications for CSF examination are included in table 2.

DIAGNOSIS

Despite several reports of unusual serologic responses in HIV-infected patients, the diagnosis and interpretation of the results of both treponemal and nontreponemal serologic tests for syphilis should be the same in HIV-infected patients as in the general population [38]. Syphilis can be accurately diagnosed with serologic tests in the majority of patients. However, direct testing methods, such as dark-field microscopic examination, direct fluorescent antibody-treponema pallidum (DFA-TP), and PCR, should be considered when the diagnosis of syphilis cannot be confirmed. Unfortunately, the dark-field examination requires special equipment and training and is not suitable for oral or rectal samples because of the potential presence of nonpathogenic spirochetes in such specimens, and DFA-TP is no longer widely available. Therefore, empirical treatment may be required in many clinical situations. To overcome this problem, researchers have developed a multiplex PCR for the etiologic evaluation of genital ulcer disease that has demonstrated sensitivities of 100%, 98%, and 91% for the detection of herpes simplex virus, *Haemophilus ducreyi,* and *Treponema pallidum,*

Table 2. Suggested indications for CSF examination in patients with concurrent syphilis and HIV infection.

Neurologic, ophthalmic, or otologic signs or symptoms
Evidence of active tertiary syphilis
Treatment failure (defined as recurrence or persistence of symptoms, lack of a 4-fold decrease in nontreponemal test titers after treatment at 12 months in early syphilis or 24 months in late syphilis, or a 4-fold increase in nontreponemal test titers at any time after treatment)
Late latent syphilis or syphilis of unknown duration

Table 3. Recommended treatment and follow-up for syphilis in HIV-infected patients.

Presentation	Recommended treatment	Alternative treatment[a]	Follow-up
Primary, secondary, or early latent syphilis	Benzathine penicillin G (2.4 million U in a single intramuscular dose)	Doxycycline (100 mg orally twice per day for 14 days), tetracycline (500 mg orally 4 times per day for 14 days), or ceftriaxone (1 g intravenously or intramuscularly once per day for 10 days)	Additional visit at 1 week with repeated serologic testing at 1, 3, 6, 9, and 12 months
Late latent syphilis, syphilis of unknown duration, or tertiary syphilis	Benzathine penicillin G (2.4 million U intramuscularly per week for 3 consecutive weeks); patient must restart treatment regimen if >14 days elapse between doses	Doxycycline (100 mg orally twice per day for 28 days) or tetracycline (500 mg orally 4 times per day for 28 days)	Additional visit at 1 week with repeated serologic testing at 3, 6, 9, 12, and 24 months; analysis of a CSF specimen
Neurosyphilis, syphilitic eye disease, or syphilitic auditory disease	Aqueous crystalline penicillin G (18–24 million U per day, administered every 4 h or by continuous infusion, for 14 days), followed by 1 dose of benzathine penicillin G (2.4 million U intramuscularly)[b]	Procaine penicillin (2.4 million U intramuscularly per day for 14 days) plus either probenecid (500 mg every 6 h for 14 days) or ceftriaxone (2 g intravenously or intramuscularly per day for 14 days), followed by 1 dose of benzathine penicillin G (2.4 million U intramuscularly)[b]	Repeated CSF analysis at 6 months and every 6 months subsequently, until the findings are normal

[a] Alternative regimens have not been well studied in HIV-infected patients; the use of these therapies must be undertaken with caution and careful follow-up.
[b] Some experts recommend benzathine penicillin G (2.4 million U intramuscularly per week for 3 weeks).

respectively [41]. More recently, a PCR technique using unique regions of the DNA polymerase I gene of *T. pallidum* proved to be useful detecting treponemes in multiple clinical samples (including blood, CSF, amniotic fluid, and genital ulcer specimens) [42, 43]. With a reported limit detection of 1–65 organisms, this technology has shown to be sensitive (sensitivity, >90%) and specific (specificity, >95%) [41, 42].

Other new technologies for the diagnosis of syphilis are also under evaluation and increasingly being used. A nontreponemal test that uses the EIA format (SpiroTek Reagin II EIA; Organon Teknika) has been recently found to be more sensitive (93% vs. 86%) and equally specific, compared with traditional RPR [44]. Contrary to all the other nontreponemal technologies currently available (RPR and the VDRL test), the EIA technology allows automation, enabling the screening of a large number of samples. Similarly, several new treponemal tests (including several rapid point-of-care tests) have shown excellent performance by using preparations of recombinant *T. pallidum* antigens [45–48]. One of those tests, a highly sensitive (95.4%) and specific (99.9%) antigen-based chemiluminescence immunoassay, is being successfully used for the diagnosis of syphilis in blood banks, but it has not yet been tested in other settings [49, 50].

Given the increasing rates of syphilis among HIV-infected patients, and given the potential clinical and public health implication of concordant HIV infection and syphilis, routine periodic screening (at least annually and 2–4 times yearly among high-risk groups, such as MSM) is strongly recommended. HIV testing is critical for all patients with a new diagnosis of syphilis [38].

TREATMENT

Once the diagnosis of syphilis has been established, HIV-infected patients should be treated in accordance with the same recommendations as for HIV-uninfected patients (table 3) [38]. Benzathine penicillin G (Bicillin LA) continues to be the drug of choice for all stages of syphilis in HIV-infected patients. HIV-infected patients with incubating, primary, secondary, or early latent syphilis and with no clinical evidence of neurologic, ophthalmologic, or otologic involvement should be treated with a single dose of benzathine penicillin G (2.4 million U) administered intramuscularly.

On the basis of the theoretical benefit of prolonged exposure to therapeutic doses of penicillin, some experts have recommended an extra 2.4 million–U dose of benzathine penicillin G administered weekly for 2 extra weeks [38, 51]. Limited data suggest that there is no difference between standard and prolonged regimens, and it is not our practice to recommend extended regimens for patients with concordant HIV infection and syphilis [52].

Although it is reasonable to administer alternative treatments, such as doxycycline, tetracycline, and ceftriaxone, to HIV-uninfected patients, very limited data exist for HIV-infected patients. In a recent case-control study, Ghanem et al. [53] found no difference in the outcomes of 34 patients with

early syphilis treated with doxycycline, compared with 73 patients treated with benzathine penicillin G. Although a small number of HIV-infected patients were included in this retrospective study (2 in the doxycycline group and 10 in the penicillin group), no treatment failures were reported among subjects treated with doxycycline. Similarly, in another study of 76 patients with syphilis (11 of whom had concordant HIV infection) treated with either penicillin or doxycycline, Long et al. [54] found similar success rates in both treatment arms (95% vs. 89%). Although the number of HIV-infected patients was very small, HIV status did not affect syphilis treatment outcomes [54]. Ceftriaxone has been recently compared with intravenous penicillin G for the treatment of neurosyphilis in 30 HIV-infected patients [55]. Similar improvements in the CSF-VDRL titer, CSF WBC count, and CSF protein concentration were found between the 2 groups [55]. Although, these and other studies suggest that doxycycline and cephalosporins might be effective alternatives to penicillin, the limited data available preclude the recommendation of these drugs for routine therapy in HIV-infected individuals [53, 54]. Recently, azithromycin was also suggested as a promising alternative oral agent for the treatment of early syphilis [56]. Unfortunately, high levels of resistance have been reported in several major cities (up to 80% in San Francisco), making it impossible to recommend this agent for empirical treatment [57, 58]. Furthermore, a clinical trial of azithromycin versus penicillin for the treatment of sexual contacts of persons with infectious syphilis was terminated early because of the high rate of treatment failure in the azithromycin arm [59].

Regardless of the drug selected for the treatment of patients with syphilis, a 4-fold decrease in nontreponemal titers (e.g., from 1:64 to 1:16) by 6–12 months of follow-up is considered an appropriate response to therapy [38]. Consequently, the slower serologic improvement after treatment of HIV-infected patients has been the basis for presumed increased rates of treatment failure reported in several studies (~20% in HIV-infected patients vs. 5% of patients from the general population at 6 months of follow-up) [30, 60, 61]. However, given that previous syphilis, new syphilis, and individual host factors affect nontreponemal titers, the clinical significance of a lack of an appropriate decrease in these titers remains unknown. Lack of follow-up (which is recommended at 1, 3, 6, 12, and 24 months after treatment but only occurs for 20%–40% of patients) further complicates decisions regarding when to re-treat patients who do not respond serologically [60, 62]. We recommend observation of the serologic response to treatment of HIV-infected patients for up to 12 months for those with early syphilis and for up to 24 months for those with late syphilis before considering therapy to have failed. However, if nontreponemal titers increase or if clinical symptoms develop at any point, treatment failure or reinfection should be considered, and patients should be reassessed and treated appropriately. If additional follow-up cannot be ensured, re-treatment is also recommended at an earlier time [38, 63].

MANAGEMENT OF SEX PARTNERS AND PARTNER NOTIFICATION

The notification of recent sex partners of patients with syphilis—and, in particular, of patients with concordant HIV infection—is a critical component of disease prevention and control in the United States. Early identification and treatment of contacts can potentially prevent the continued spread of both infections. Therefore, persons exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively with benzathine penicillin (2.4 million U intramuscularly) once. Persons who were exposed >90 days preceding the diagnosis of early syphilis in a sex partner should also be treated presumptively if serologic results are not available or follow-up is uncertain. Other sex partners are considered to be at risk for infection and should be contacted and evaluated clinically and serologically.

Partner notification can be difficult when information about sex partners is limited. In this regard, the immediate access to large, anonymous sexual networks provided through the Internet has challenged traditional partner notification strategies. However, it has also provided potential opportunities for intervention. During a recent syphilis outbreak that involved 7 MSM in San Francisco who met in an online chat, electronic notification of the cluster was provided to hundreds of chat room users [64]. Despite very limited contact information, the Department of Public Health was able to notify and treat 42% of the named sex partners [64]. Using a similar approach, the Los Angeles Department of Public Heath was able to contact and evaluate 50% of the sex partners of 2 patients with syphilis who belonged to another Internet-based sexual network [65]. Similarly, anonymous partner notification through E-mail or E-cards is currently being used by several public health agencies in the United States and provides an alternative to standard partner notification services [66].

Public health efforts targeting Internet users have also proved to be useful in increasing awareness about syphilis [67–69]. The use of banner ads has been successful in increasing the knowledge of syphilis symptoms and transmission and in promoting testing [67]. An online syphilis testing service that allows people to print out the laboratory requisition slip, have their blood samples obtained, and receive their result online has been available in San Francisco since June 2003 [69]. During the first year of this service, 544 visitors per week used the Web site. On average, 12 laboratory requisition forms were downloaded, and 4 people had blood drawn each week, leading to the detection and treatment of 6 new cases of syphilis this year [69]. Given the success and potential of Internet-based interventions,

clinicians should be aware of health department efforts to use the Internet to contact partners, to promote awareness of and testing for syphilis and HIV infection, and for partner management [70].

CONCLUSIONS

Despite several advances in the understanding of the interaction between HIV infection and syphilis achieved during the past few years, the clinical treatment of coinfected patients remains challenging. Recent changes in the epidemiology of patients who have concordant syphilis and HIV infection will require innovative public health strategies to control these new and resurgent epidemics. Additional studies to establish the population most likely to benefit from examination of CSF specimens and the best treatment approach in neurosyphilis are required. Clinicians are key participants in syphilis control, because they must educate patients, counsel them in sexual risk reduction, and routinely and frequently screen those at increased risk.

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