AIDS Rev. 2008;10:85-92

Effect of HIV Infection on the Course of Syphilis

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Abstract

Syphilis has been a public health problem for centuries. Syphilis and HIV form a dangerous combination: syphilis significantly increases the risk of contracting HIV infection, and HIV can alter the natural course of syphilis. Despite a better understanding of the interaction between these two diseases, many controversies persist. The incidence of syphilis has increased among HIV-infected patients both in Europe and in the USA, and especially in the homosexual/bisexual transmission group. We discuss the interaction between HIV/AIDS and syphilis in a review of the most recent literature, focusing particularly on the diagnosis, treatment, and follow-up of HIV-infected patients with syphilis. Early diagnosis of syphilis in HIV-infected patients requires awareness among both patients and clinicians. Early treatment of syphilis is crucial as it reduces the risk of transmission.

(AIDS Rev. 2008;10:85-92)

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Key words

Syphilis. TPHA. HIV. STD. MSM.

Introduction

Despite more than two decades of fundamental research and clinical studies of coinfected patients, the complex interaction between syphilis and HIV infection remains controversial[1-6].

The incidence of syphilis has increased since 2000 in Europe and the USA, notably with a rise in the frequency of early syphilis among HIV-infected patients. After the 1940s, the incidence of syphilis was relatively stable, even during the early stages of the HIV pandemic in the 1980s. New epidemics involving men who have sex with men (MSM) have since been detected in most major U.S. and European cities[7-13]. In the USA the rate of primary and secondary syphilis increased from 2.1 cases per 100,000 persons in 2000 to three cases per 100,000 persons in 2006[7], and MSM accounted for about 65% of all persons with primary or secondary syphilis[14-17]. Recently, the Centers for Disease Control (CDC) reviewed the clinical course of symptomatic early neurosyphilis among HIV-infected MSM[18]. The reasons for this rapid increase in the rate of syphilis among HIV-infected MSM are complex, but it clearly suggests a decrease in safer sex practices[19]. Other contributory factors include the increased use of recreational drugs, internet dating, and the increased frequency of HIV serosorting[20,21]. Oral sex, sometimes preferred in order to reduce the risk of HIV transmission, is a practice at risk of syphilis. Epidemiologic data show that syphilis and genital ulcers are associated with an increased risk of HIV acquisition[6,22-25].

Some case reports suggest that syphilis may influence the natural course of HIV infection (reviewed[6,26-29]). Others suggest that unusual clinical manifestations of syphilis or neurosyphilis may be more frequent in patients with HIV infection, and that the course of syphilis may be more rapid[6,30-35].

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Atypical features of syphilis in HIV-infected patients are reported in table 1. In summary, HIV/syphilis coinfection can be associated with the following atypical features:

– Higher titer rapid plasma reagin (*Treponema pallidum* hemagglutination assay, TPHA, or rapid plasma reagin, RPR).

– Multiple or deeper chancres.

– Overlap of features of primary and secondary syphilis.

– More rapid progression to tertiary syphilis.

– Ocular syphilis.

– False-negative syphilis serology.

– Clinically important neurologic disease and a shorter latency period before meningovascular syphilis.

– Lesser efficacy of standard therapy for early syphilis.

However, recent review articles show that few of these features have been confirmed in large observational studies[6,30].

Also, the diagnosis of syphilis may be more complicated in HIV-infected patients, and this calls for: i) careful physical examination of HIV-infected persons; ii) closely monitoring the treatment for syphilis in HIV-infected patients; iii) identification and treatment of sexual partners.

The frequency of HIV/syphilis coinfection depends on the prevalence of the two infections in a given patient group and on individual risk factors. A U.S. review of 30 studies[6] showed an overall median HIV seroprevalence of 15.7% in patients with syphilis (27.5% in men; 12.4% in women) and an odds ratio for HIV infection of 8.8 in men and 3.3 in women with syphilis relative to patients without syphilis.

The baseline prevalence of syphilis was 13% in a Spanish study of 1,161 HIV-seropositive patients, contrasting with 1.33% (151/11,368) found by the German AIDS Study Group (reviewed[31]).

Also, genital ulcers associated with syphilis can increase the risk of HIV transmission[8,23-25,31]. Syphilis coinfection may have facilitated HIV transmission in 545 American couples with discordant HIV serostatus, representing a cost of US$ 113 million[36]. Recent estimates suggest that the reduction in the incidence of syphilis and gonorrhea between 1990 and 2003 saved five thousand million US$[37].

The situation was similar in France and the USA to that in other European countries, where an upsurge in syphilis has been noted since 1999[1,5-8]. Most patients are homosexual or bisexual men, and a large proportion of them are HIV seropositive. In Eastern Europe the upsurge in syphilis predates that observed in western countries and is strongly linked to prostitution, mainly affecting women and intravenous drug users[13]. A resurgence of syphilis has also been observed among heterosexuals[6,38,39].

In this article we discuss the interaction between syphilis and HIV infection in an updated review.

French experience

In our experience between 1 January 2000 and 30 June 2004, 110 cases of syphilis were identified in the database including 2,865 HIV-infected patients[40].

The number of cases increased from eight in 2000 to 26 in 2001 and 40 in 2002. The upsurge peaked in the second half of 2002, with 28 new cases diagnosed between 1 June and 31 December 2002. After January 2003, the number of new cases started to fall gradually, from 20 in the first half of 2003, to nine in the second half of 2003 and seven in the first half of 2004.

Only two of the 100 patients with active syphilis were women. Among the 98 male patients, 87 (89%) were homosexual and seven (7%) were bisexual.

HIV infection was diagnosed at the same time as the current episode of syphilis in 11% of cases. Seventy-seven percent of the patients had already started antiretroviral therapy before the diagnosis of syphilis, on average five years previously (range 0-17 years, standard deviation ± 3.3 years). After January 2001, the number of new cases of syphilis diagnosed in our department increased gradually, notably among HIV-infected patients, peaking in the second half of 2002. Twenty-eight cases of syphilis were diagnosed in this latter period, exceeding the total number of cases diagnosed in 2001. The increase was due to symptomatic syphilis and also to latent syphilis, the frequency of which increased 2.75-fold between 2001 and 2002. These data probably reflect the impact of a syphilis screening campaign conducted in 2002. We diagnosed only seven new cases in the first half of 2004[40].

More than 90% of the patients in this study were men, and a large proportion of them were homosexual or bisexual. Several indicators point to an increase in at-risk sexual behaviors among male homosexuals after 2000, involving both occasional and regular partners. In the 2002 French Baromètre Gay survey of public meeting places frequented mainly

by homosexual and bisexual men, 53% of respondents stated they had had more than 10 sexual partners in the previous 12 months, while half said they had had unprotected oral sex, and one-third unprotected anal penetration on at least one occasion[41]. One in ten of the respondents were HIV-seropositive, while one-quarter were unaware of their HIV serostatus. These behaviors appear to be continuing: the 2004 Gay Press survey, published in June 2005 by the Institut de Veille Sanitaire (InVS) and the national research agency for HIV/AIDS and viral hepatitis (ANRS), showed a reduction in the use of condoms for oral sex (7.2 vs. 13.5% in 1997) and an increase in unprotected anal sex (35.8% of respondents said they had had unprotected anal sex in the previous 12 months, compared to 33% in 2002) (available on www.anrs.fr).

The resurgence of syphilis is not an isolated phenomenon, as other acute sexually transmitted diseases (STD) are also becoming more frequent. More than half the patients concerned are HIV-seropositive.

Clinical manifestations of syphilis in HIV-infected patients

At diagnosis, the most frequent clinical manifestation of syphilis observed in our cohort was secondary skin rash (35%). The rash was macular (first rash) or papular (second rash) and was usually isolated. It was associated with other secondary clinical signs in 8% of cases (headache, fever, and adenopathy or organ involvement).

Primary syphilis (genital, anal, or oral chancre) was diagnosed in 25% of cases. Four patients had signs of both primary and secondary involvement at diagnosis (primo/secondary forms). Two patients had neuromeningeal syphilis. One-quarter of patients were asymptomatic and therefore had a latent form of syphilis. It was difficult to distinguish early latent forms from late latent forms because only 48% of the patients concerned reported evidence of being infected less than one year previously[40].

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[32]. Although highly unusual, malignant secondary syphilis has been described to be more frequent during advanced HIV disease[6,24,42,43].

As discussed above, the management of neurosyphilis in an HIV-infected patient is controversial. Early reports suggest that HIV infection accelerates and changes the course of neurosyphilis[44-46]. However, the interpretation of cerebrospinal fluid (CSF) findings in the setting of HIV infection is particularly complex and discussed here.

Early diagnosis of syphilis

Early diagnosis is crucial for controlling syphilis, and this requires good physician awareness. Syphilis may be missed during the primary phases (oropharyngeal or anal lesions only) and also in the secondary phase, yet any delay in treatment can prolong the period of contagiousness. Clinicians should screen all sexually active patients with HIV infection for asymptomatic syphilis[6,31]. Routine periodic screening is strongly recommended, at least 2-4 times yearly among active, high-risk, HIV-infected patients. During the diagnosis process, a risk assessment of sexual practices must be made, including a questionnaire regarding symptoms of syphilis that include dermatologic, neurologic, ocular or auditory manifestations. Careful examination of the skin, scalp, oropharynx and genital or anal area, as well as a complete neurologic examination should be performed in every patient[30].

Serologic responses

Unusual serologic responses have been observed in HIV/syphilis-coinfected patients. The majority of reports involved an increased rate of false-negative serologic tests in both primary and secondary syphilis[47]. The prozone phenomenon may cause a false-negative non-treponemal test result, usually during secondary syphilis, when a high concentration of treponemal antigens hinders the formation of detectable antigen/antibody complexes[48]. Other differences in the serologic responses observed in HIV-seropositive patients include a high rate of failure to clear non anti-treponemal antibodies after therapy, and seroconversion to negative of specific treponemal tests after treatment[6,49,50].

Most specialists believe that both treponemal and non-treponemal serologic tests for syphilis can be interpreted in the usual manner for the majority of coinfected patients[31]. When clinical findings are suggestive of syphilis despite negative serologic tests, alternative

Table 1. Atypical features of syphilis in the HIV-seropositive patients

Signs, symptoms and variation reported in HIV-infected patients	Reference
Higher rate of symptomless primary syphilis.	Lynn, Rolfs, Hall
Primary syphilis with multiple or deeper chancres.	Hutchinson
Higher rate of secondary disease.	
Overlap of primary and secondary stage features of syphilis.	Lynn, Hall
Increased rate of early neurologic and ophthalmic involvement.	Lynn, Hall
More rapid progression to tertiary manifestation.	Hutchinson
Report of false-negative serology in both primary and, less commonly, in secondary syphilis.	
Reduced efficacy of standard therapy for early syphilis.	Lynn
Relapse is more frequent.	Rolfs, Hall, Malone
Jarisch-Hersheimer reaction is more frequent.	
Normalization of CSF values after treatment: delayed.	Rolfs,
Prozone phenomenon more frequent.	Marra, Lynn

tests (e.g. biopsy or dark-field microscopic examination) can be considered.

Despite several reports of unusual serologic responses in HIV-infected patients, the interpretation of both treponemal and non-treponemal serologic tests for syphilis seems to be the same in HIV-infected and uninfected patients[31]. If biopsy specimens are required and do not reveal spirochetes despite clinical signs of syphilis, presumptive treatment for early syphilis may be initiated and followed with serologic tests two weeks later to detect a delayed antibody response[1,6,31]. Syphilis can be accurately diagnosed with serologic tests in the majority of patients. Direct methods such as PCR and dark-field microscopic examination can be used when the diagnosis of syphilis cannot be confirmed by serologic tests. However, these tests usually are unavailable in routine practice and the dark-field microscopic is relatively insensitive[30].

Diagnosis of neurosyphilis

The diagnosis of neurosyphilis is complicated by the difficulty of distinguishing between neurologic disorders caused by *T. pallidum*, that may affect the brain, spinal cord or peripheral nerves, and those caused by HIV itself or by opportunistic CNS pathogens[51,52]. In our experience, only nine of the 100 patients had lumbar puncture, two for treatment failure and seven because neurologic signs were present at initial diagnosis[40]. The reported prevalence of neurosyphilis in HIV-infected patients can be as high as 23.5-40%, compared to 10% in HIV-seronegative patients with untreated syphilis[31].

Approximately one-third of patients with early syphilis have neurologic involvement[6]. A correlation between advanced HIV disease and abnormal CSF findings related to neurosyphilis has recently been reported[53]. Nevertheless, HIV infection is clearly associated with an increased risk of neurosyphilis, and especially early neurosyphilis. A recent CDC report[18] reviewed 49 cases of early neurosyphilis among HIV-seropositive MSM. Neurosyphilis is a serious disease that can involve substantial utilization of healthcare resources and persistent disabilities for HIV-coinfected patients. In the CDC case series, 75% of the patients reported visual disturbances, 12% had acute symptomatic meningitis, and 30% had persistence of neurosyphilis symptoms after six months of follow-up[18]. The Venereal Disease Research Laboratory/Rapid Plasma Reagin (VDRL/RPR) is the principal serologic test approved for the diagnosis of neurosyphilis on CSF specimens[18,54]. Neurosyphilis may occur in the early post-primary stage of syphilis or after a gap of many years.

Increased rates of early neurologic and/or ophthalmic involvement have been reported in HIV/syphilis coinfection (Table 1). Higher cell counts, higher protein levels, and lower glucose levels have been reported in the CSF of HIV-coinfected patients, but their clinical significance is unclear[55-57]. Recently, Libois, et al. reviewed the cases of 112 HIV-infected patients with syphilis who underwent lumbar puncture. The diagnosis of neurosyphilis was based on a CSF white cell count ≥ 20/µl and/or a reactive CSF-VDRL, and/or a positive intrathecal *T. pallidum* antibody (IT TPA index). Twenty-six of the 112 patients had neurosyphilis. Multivariate analysis confirmed that a serum RPR titer

Table 2. Indications for cerebrospinal fluid examination (lumbar puncture) in the management of syphilis in HIV1 (adapted from Hall and from Zetota and Klausner)[6]

Infection of unknown duration.
Late latent syphilis.
Neurologic symptoms including meningeal symptoms or cranial nerve involvement.
Ophthalmic involvement (uveitis; retinitis, optic neuritis, etc.).
Primary or early latent with RPR/VDRL < 1:32 and CD4 cell count < 350/mm^3.
Any stage with RPP/VDRL > 1:32.
Treatment failure defined as recurrence or persistence of symptoms or lack of a fourfold decrease in non-treponemal test titers at 12 months (early syphilis) or 24 months (late syphilis) after optimal therapy, or a fourfold increase in non-treponemal test titers at any time.
Evidence of active tertiary syphilis.

RPR: Rapid Plasma Reagin; VDRL: Venereal Disease Research Laboratory.

≥ 1:32 indicates lumbar puncture in HIV-coinfected patients[55]. A significant association was found between neurosyphilis and serum RPR titers of ≥ 1:32 and CD4 cell counts < 350/mm^3. On the basis of these results, some guidelines now recommend lumbar puncture and CSF examination for HIV-infected patients with RPR titers > 1:32 or CD4 cell counts < 350/mm^3 (Table 2).

The use of lumbar puncture to diagnose neuromeningeal syphilis is controversial in HIV-infected patients who have no neurologic or ophthalmologic signs on physical examination[55-60]. Suggested indications for CSF examination in patients with syphilis and HIV coinfection are summarized in table 2. American guidelines recommend lumbar puncture at six months in patients with serologic failure, or late latent or undetermined syphilis, or relevant neurologic signs. If the initial lumbar puncture is positive, controls are recommended at 6, 12 and 24 months[54].

Treatment for syphilis

In our experience, treatment was clinically and biologically effective at six months in 91% (n = 74) of the assessable patients[40]. The most common treatment (85% of patients) was intramuscular benzathine penicillin G 2.4 MU, given three times one week apart in 65% of cases, twice at a one-week interval in 15% of cases, and only once in 5% of cases. Biological cure was achieved in 74/81 (91%) of the assessable patients.

Intramuscular benzathine penicillin G continues to be the drug of choice for all stages of syphilis in HIV-infected patients, and was the most common treatment in our study (85% of patients). The HIV-infected patients without evidence of neurologic, ophthalmologic or otologic involvement may be treated with a single dose of benzathine penicillin G 2.4 million IU administered intramuscularly[14-16,54,61-63]. Some authors recommend one or two extra doses of benzathine penicillin 2.4 million IU, but there are few data on the efficacy of these extended regimens[6,31]. Doxycycline, azithromycin and cephalosporins are presented as promising alternatives for the treatment of early syphilis, but data on HIV-infected patients are limited[64,65].

Relapses and recurrences were not more frequent in immunodeficient patients in our study, most of whom received three intramuscular injections of benzathine penicillin G[40,66-68].

Some patients relapsed despite biological signs of treatment efficacy. This warrants long-term serologic follow-up. A four-fold reduction in the VDRL titer at six months seems to be a good prognostic factor, but does not always signify that the patient is cured. Treatment can only be considered fully effective when all serologic signs of infection disappear. It is recommended to perform a lumbar puncture and to re-treat patients in whom the non anti-treponemal antibody titer shows a four-fold re-increase, or when a fourfold decrease in non-treponemal test titers is not obtained after 12 months of optimal treatment for early syphilis (24 months for late syphilis; Table 2).

Treatment of syphilis in HIV-infected patients consists of standard stage-appropriate treatment as summarized in table 3. Clearance of neurosyphilis is problematic in HIV-infected patients, poorer responses being observed in patients with low CD4$^+$ cell counts and/or uncontrolled HIV viral load. The recommended treatment for early neurosyphilis is aqueous crystalline penicillin G, 18-24 million units per day, administered as 3-4 million units intravenously every four hours or by continuous infusion, for 10-14 days, regardless of HIV status[54].

Management of sex partners

In our experience, secondary contacts were only sought in 14% of cases. There are no guidelines in France on the management of partners of STD patients and partner notification or analyses of sexual networks

Table 3. Recommended treatment regimens for syphilis and neurosyphilis*

Primary, secondary, and early latent infection	
Treatment	Benzathine penicillin G, 2.4 MU IM in a single dose
Additional considerations	Alternative regimens (e.g. tetracyclines) are not well studied in HIV infection; careful follow-up recommended. Azithromycin not recommended for treatment of syphilis. Follow-up includes clinical evaluation at 1-2 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 into 3 weekly IM doses (2.4 MU per dose). Otherwise, treat for neurosyphilis, as below.
Additional considerations	Alternative regimens (e.g. tetracyclines) are not well studied in HIV infection; careful follow-up is essential when they are used to treat late infection. Follow-up includes clinical and serologic evaluation at 6, 12, 18, and 24 months after treatment.
Neurosyphilis (including ophthalmic or ocular involvement	
Treatment	Aqueous crystalline penicillin G, 18-24 IV MU per day (i.e., 3.4 MU every 4 hours) or continuous infusion 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 4 times per day, both for 10-14 days; another (less well studied) alternative is ceftriaxone 2 g IV daily for 14 days. Most experts recommend benzathine penicillin G, 7.2 MU, divided in 3 weekly IM doses (2.4 MU per dose), after completion of one of the above regimens.
Penicillin-allergic and pregnant patients	
Considerations	Alternatives to penicillin (e.g. tetracyclines) 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 or desensitization to facilitate therapy with penicillin is recommended in pregnant patients and for the treatment of latent syphilis and neurosyphilis in other patients with HIV infection.

*Recommended by the U.S. Centers for Disease Control and Prevention; other recommendations as indicated[8,14].
CSF: cerebrospinal fluid; IM: intramuscularly; IV: intravenously; LP: lumbar puncture; MU: million units.

are uncommon. Identification and screening of sexual partners is important for controlling syphilis in the population and, in particular, among HIV-infected patients. The notification of recent sex partners of patients with syphilis is a critical component of disease control and prevention in the USA. Identification of recent cases and/or partners notification have the potential to stop the spread of the epidemic[30,69]. A high rate of asymptomatic syphilis has been detected among HIV-infected patients in primary care settings and routine screening could be effective in outpatients[70-73]. American guidelines recommend that all HIV-infected patients be screened for syphilis and other STD every 3-6 months and a single injection of benzathine penicillin G for contacts who had sex less than 90 days before the diagnosis of syphilis in the partner[54].

Conclusion

This review highlights the resurgence of syphilis in HIV-infected patients, linked mainly to a resumption of at-risk behaviors among men who have sex with men. Early diagnosis of syphilis relies on awareness among both persons at risk and clinicians.

Sexual contacts must be identified and treated if necessary, as they may infect new partners or reinfect regular sex partners. Finally, long-term serologic follow-up of treatment efficacy is necessary,

with a new treatment course if serologic markers rise significantly.

Acknowledgments

David Young for editorial assistance and Sandrine Thevenet for database management and clinical data, and Nathalie Jouanne for helping in manuscript typing.

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