Similar serological response to conventional therapy for syphilis among HIV-positive and HIV-negative women

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Abstract

***Objectives*—To compare characteristics of syphilis serological reactivity in HIV positive (+) and HIV negative (−) female sex workers, as well as the serological response to therapy after treatment with intramuscular benzathine penicillin, 2·4 million U weekly, for three consecutive weeks.**

***Methods*—Rapid plasma reagin (RPR) and *Treponema pallidum* haemagglutination assay (TPHA) results of 72 HIV-positive and 121 HIV-negative women reactive in both tests were assessed. The response to therapy was prospectively monitored with quantitative RPR serology in 47 HIV-positive and 73 HIV-negative patients. Cumulative probabilities of becoming nonreactive by RPR were compared at six months, one and two years after therapy.**

***Results*—At enrolment, the geometric mean titres of RPR and TPHA were lower in HIV-positive patients (RPR, 1:2.6) than in HIV-negative patients (RPR, 1:3.8; $p < 0·01$). The evolution over time of RPR titres was similar among HIV-positive patients as compared to HIV-negative patients. Among patients with an initial RPR titre of < 1:8, 53% of HIV-positive and 44% of HIV-negative patients became RPR negative two years after therapy. Among patients with an RPR titre of 1:8 or greater at enrolment, 83% of HIV-positive and 90% of HIV-negative patients had reached at least a fourfold decline of RPR titres two years after therapy.**

***Conclusions*—Syphilis serology findings (both RPR and TPHA) may be altered in the presence of HIV infection, but the serological response to therapy was similar in HIV-positive and HIV-negative patients.**

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Introduction

Since the emergence of the AIDS epidemic, syphilis has attracted renewed attention. Not only has it been shown that genital ulcers facilitate the transmission of human immunodeficiency virus (HIV),[1–4] but there is also considerable concern about the impact of HIV infection and related immune deficiency on the natural history of syphilis.[4 5] A more aggressive course and unusual clinical presentations have been suspected in HIV-seropositive individuals, and neurological complications have been reported to be more frequent and to occur at an earlier stage in HIV-positive subjects than in HIV-seronegative patients.[6–8] The decreased immune functions of HIV-positive patients may alter the response to treatment, especially to the single dose therapy recommended for primary and secondary syphilis.[9 10] Serological tests for the diagnosis of syphilis and for monitoring of antimicrobial therapy may also be impaired, although this again remains controversial.[11–13] Finally, although serological monitoring of syphilis therapy is recommended, the evolution of serological responses is not well documented, even in patients without HIV infection.

In order to assess whether the serological response to treatment of syphilis in HIV-positive subjects is impaired, we compared the evolution of RPR titres after treatment in HIV-positive and HIV-negative women with reactive syphilis serology in Kinshasa, Zaire.

Methods

Study population

Study participants were female sex workers who attended the Women's Health Centre of Matonge in Kinshasa, Zaire, and gave informed consent. Initially, a cross sectional survey was performed among 1233 women, to document prevalence rates of various sexually transmitted diseases (STDs).[14] Subsequently a cohort study was established to study the impact of STD control and condom promotion on the sexual transmission of HIV.[15] Women with both positive rapid plasma reagin (RPR) and *Treponema pallidum* haemagglutination (TPHA) serology at enrolment were considered to have active syphilis. The history of earlier syphilis treatment was unknown.

Study design

All women with a reactive syphilis serology, enrolled in the larger cohort study, were treated with intramuscular injections of benzathine penicillin G, 2·4 million units weekly for three consecutive weeks according to the guidelines of the Centers for Disease Control and the World Health Organization.[9 10] The evolution of RPR titres in HIV-positive patients was compared with those among

HIV-negative patients after six, 12 and 24 months.

At the enrolment visit consenting women answered a questionnaire regarding demographic characteristics, gynaecological history, prostitution, sexual practices and medical history. A gynaecological examination was performed and samples were taken for detection of STD. Blood was drawn for serology of HIV, syphilis and *Haemophilus ducreyi* infection. Women in whom both RPR and TPHA were positive were considered to have active syphilis, and were asked to participate in a prospective study to monitor the response to treatment. Patients were asked to return for monthly follow-up visits for health education, condom distribution and management of STD, and each third month blood was drawn for HIV and syphilis serology. Only patients who were followed up for at least six months were included in the analysis of therapy outcome. For this analysis, patients were divided into two groups by RPR titre at enrolment, including women with an RPR titre of less than 1:8, and women with an RPR titre of 1:8 or more. Adequate serological response to therapy was defined as an RPR result becoming negative in the first group, or the RPR titre showing a fourfold decline in the second group. The study was approved by the national ethics committee of the Ministry of Health of Zaire.

Laboratory procedures

Serology was performed at the laboratory of Projet SIDA in Kinshasa. The study tests were commercially available kits. The rapid plasma reagin (RPR) test from Becton-Dickinson, Baltimore, Maryland and the *Treponema pallidum* haemagglutination (TPHA) test from Fuji-Rebio, Japan were used for syphilis serology. Sera were tested for HIV antibody by EIA (Vironostika Organon Tecknika, the Netherlands) and positive EIA results were confirmed by Western blot analysis (Du Pont de Nemours, Wilmington, Delaware). Diagnosis of other sexually transmitted diseases was performed at the same laboratory, as described elsewhere.[14]

Statistical analysis

The Chi square, Fisher exact test, the *t* test and the Wilcoxon 2-sample test were used as appropriate. The evolution of the RPR titres in the different groups was compared using the actuarial life table method.[16] If a patient did not present at one or more of the intermediate visits (that is, month 6 and/or month 12), then the latest known RPR titres were considered for evaluation. Once a patient met the serological criteria for "adequate response", she was considered to be reacting successfully to treatment.

Table 1 Comparison of women with reactive [RPR and TPHA] to women with negative RPR at enrolment

	RPR and TPHA positive (n = 193)	*RPR test negative (n = 1040)*	*p-value*
Demographic characteristics			
Zairian nationality	96%	95%	NS
Age (years, SD)	28 (7)	25 (7)	<0·001
Never been to school	49%	33%	<0·001
Age at first sexual intercourse (years, (SD))	14 (2)	15 (2)	NS
Mean number of pregnancies (SD)	3 (2)	3 (2)	NS
One or more children died	45%	35%	0·01
One or more spontaneous abortions	17%	14%	NS
Characteristics related to prostitution			
Type of prostitution			0·02
Hotel	50%	58%	
Home	45%	35%	
Street	5%	7%	
Months in prostitution (median)	48	36	<0·001
Number of clients per week (mean, SD)	8 (8)	8 (8)	NS
Sexual practices:			
Vaginal sex (ever)	100%	100%	NS
Oral sex (ever)	20%	26%	NS
Anal sex (ever)	7%	16%	0·003
Sex during menses (ever)	62%	56%	NS
Regular condom use	8%	13%	NS
Sexually transmitted diseases			
Neisseria gonorrhoeae	19%	24%	NS
Chlamydia trachomatis	10%	14%	NS
Trichomonas vaginalis	22%	22%	NS
Candida albicans	8%	10%	NS
Presence of genital ulcer	7%	4%	NS
History of genital ulcer (last 5 yrs)	43%	39%	NS
Positive *H ducreyi* serology	87%	62%	<0·001
Pubic lice (last 5 yrs)	62%	48%	<0·001
HIV infection	37%	35%	NS

Results

Characteristics of syphilis patients at enrolment

Out of 1233 women enrolled in the cross sectional study, 193 (16%) had both positive RPR and positive TPHA results and another 151 (12%) were only TPHA positive at enrolment. Women reactive for both RPR and TPHA were slightly older, had less frequently been to school, and had worked as a prostitute for a longer time period than women with negative syphylis serology (table 1). All other variables were similar in both groups, except for a lower proportion of women with syphilis engaging in anal sex. Reported regular condom use was low in both groups: 8% among syphilis patients and 13% among the other women. The prevalence of STD at enrolment was similarly high among both groups. Genital ulcer disease (GUD) was present in 7% of syphilis patients and in 4% of the other women, but this difference was not significant. However, women with positive syphilis serology had more frequently a history of pubic lice infestation during the previous five years (62% vs 48%, $p < 0·001$), as well as antibody against *Haemophilus ducreyi*, suggestive of an earlier episode of chancroid (87% vs 62%, $p < 0·001$).

There were no differences between HIV-positive and HIV-negative study participants with respect to age, age at first sexual intercourse, time in prostitution and sexual practices, as has been described elsewhere.[14]

Table 2 shows the results of the quantitative RPR and TPHA serologies at enrolment by HIV serostatus among the 193 patients. Seventy-two patients (37%) were HIV-positive and 121 (63%) were HIV-negative. Among HIV-positive patients, 59 (82%) had an RPR titre of less than 1:8, compared to 69% in HIV-negative women ($p = 0·06$). The geometric mean titre (GMT) of the RPR results at enrolment was significantly lower among HIV-positive women (GMT 2·6) than

Table 2 Comparison of quantitative syphilis serology in HIV-positive and HIV-negative women before therapy

	HIV-positive (n = 72)	*HIV-negative (n = 121)*	*p-value*
	n (%)	n (%)	
RPR titre			
1:1	24 (33·3)	25 (20·7)	
1:2	24 (33·3)	34 (28·1)	
1:4	11 (15·3)	24 (19·8)	
1:8	5 (6·9)	20 (16·5)	
1:16	4 (5·6)	10 (8·3)	
1:32	3 (4·2)	2 (1·7)	
1:64	1 (1·4)	2 (1·7)	
1:128	0 (0·0)	4 (3·3)	
GMT*	1:2·6	1:3·8	0·01
TPHA titre			
1:80	0 (0·0)	3 (2·5)	
1:160	5 (6·9)	3 (2·5)	
1:320	6 (8·3)	1 (0·8)	
1:640	7 (9·7)	8 (6·6)	
1:1280	14 (19·4)	14 (11·6)	
1:2560	9 (12·5)	18 (14·9)	
1:5120	14 (19·4)	29 (24·0)	
1:10240	17 (23·6)	45 (37·2)	
GMT*	1:2153	1:3589	0·005

*GMT = Geometric Mean Titre.

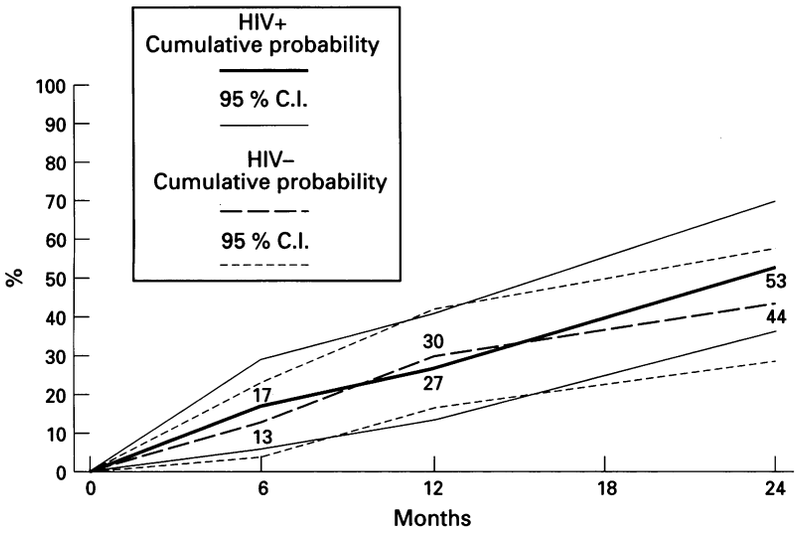

Figure 1 Cumulative probabilities of RPR-seroreversal in HIV(+) and HIV(−) women with initial RPR titre <8.

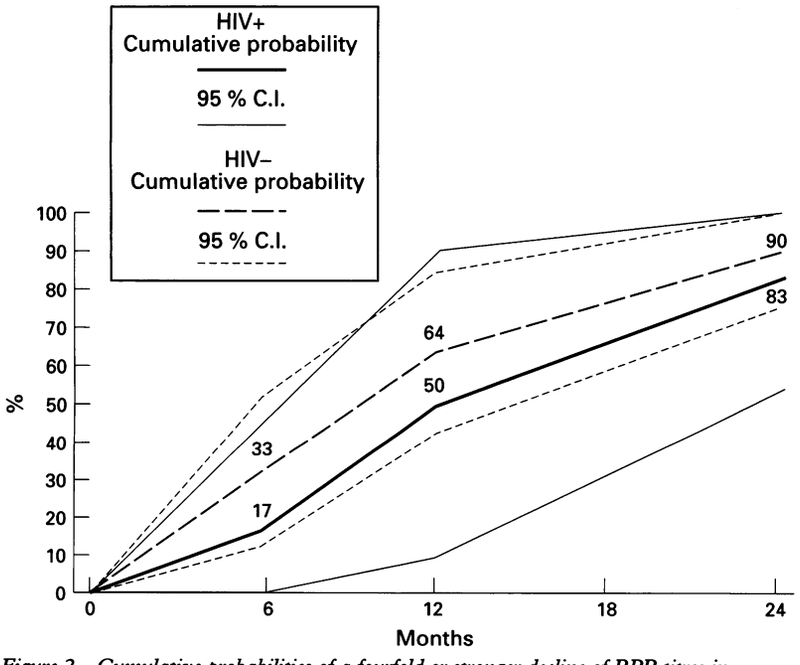

Figure 2 Cumulative probabilities of a fourfold or stronger decline of RPR titres in HIV(+) and HIV(−) women with initial RPR titre > 8.

among HIV-negative women (GMT 3·8, p = 0·01). Similarly the GMT of TPHA results in HIV-positive women was significantly lower than HIV-negative women, with 2153 versus 3589 respectively (p = 0·005).

Serological response to treatment

Longitudinal data were available for 120 participants: 47 HIV-positive (65%) and 73 HIV-negative patients (60%). The distribution of RPR titres was similar among women who participated in the longitudinal study and the 193 syphilis patients at enrolment.

Follow-up RPR titres were available from 41 HIV-positive and 52 HIV-negative patients with an RPR titre of less than 1:8 at enrolment (table 3). Negative RPR results were observed in 27% of the HIV-positive patients presenting at the six months' visit, in 15% one year after treatment, and in 39% of the women presenting after two years. Among HIV-negative patients, a negative RPR test was observed in 15%, 21% and 21%, respectively. There was no significant difference between the HIV-positive and HIV-negative women at any of the three time points (at six

Table 3 Evolution of RPR titres in HIV-positive and HIV-negative syphilis patients with an initial RPR titre of less than 1:8

RPR result	*HIV-positive n = 41 (%)*	*HIV-negative n = 52 (%)*
month 6	**(N = 26)**	**(N = 47)**
Became seronegative	7 (27)	7 (15)
⩾ fourfold decline	0 (0)	0 (0)
Stable	16 (61)	38 (81)
⩾ fourfold increase	3 (12)	2 (4)
month 12	**(N = 26)**	**(N = 38)**
Became seronegative	4 (15)	8 (21)
⩾ fourfold decline	0 (0)	2 (5)
Stable	20 (77)	22 (58)
⩾ fourfold increase	2 (8)	6 (16)
month 24	**(N = 23)**	**(N = 29)**
Became seronegative	9 (39)	6 (21)
⩾ fourfold decline	2 (9)	1(3)
Stable	12 (52)	20 (69)
⩾ fourfold increase	0 (0)	2 (7)

Table 4 Evolution of RPR titres in HIV-positive and HIV-negative syphilis patients with an initial RPR titre ⩾ 1:8

RPR result	*HIV-positive n = 6 (%)*	*HIV-negative n = 21 (%)*
month 6	**(N = 3)**	**(N = 18)**
Became seronegative	0 (0)	0 (0)
⩾ fourfold decline	1 (33)	7 (39)
Stable	2 (67)	11 (61)
⩾ fourfold increase	0 (0)	0 (0)
month 12	**(N = 5)**	**(N = 11)**
Became seronegative	0 (0)	0 (0)
⩾ fourfold decline	2 (40)	6 (55)
Stable	3 (60)	5 (45)
⩾ fourfold increase	0 (0)	0 (0)
month 24	**(N = 3)**	**(N = 5)**
Became seronegative	0 (0)	1 (20)
⩾ fourfold decline	2 (67)	3 (60)
Stable	1 (33)	1 (20)
⩾ fourfold increase	0 (0)	0 (0)

months: p = 0·2; at one year: p = 0·7; after two years: p = 0·25). Figure 1 shows the cumulative probabilities and the 95% confidence intervals (95% CI) of the RPR becoming negative at the three time points, which were similar among women with and without HIV infection.

Among women with an initial RPR titre of 1:8 or more, a fourfold or more important decline of the RPR titre was seen in 33% of HIV-positive women when presenting at the month six visit, 40% at one year and 67% at two years (table 4). The corresponding figures for HIV-negative patients were 39%, 55% and 80%, respectively. There was no significant difference at any of the three observed time points. The cumulative probabilities of attaining a fourfold or greater decline of RPR titres as presented in figure 2, were also similar for HIV-negative and HIV-positive patients at the three time points.

Discussion

Data on the response to therapy in women with syphilis and concomitant HIV infection are scarce. This study suggests that although initial RPR and TPHA titres were higher in HIV-negative compared with HIV-positive women, serological response (measured by RPR titres) to conventional therapy, is similar in both groups.

Presumptive diagnosis of active syphilis was made on the presence of a positive RPR and a positive TPHA serology. RPR titres lower than 1:8 dilutions were predominant among our study population, both in HIV-positive and HIV-negative women. Low titres are most common at the very beginning of the infection (primary syphilis), during the later stage (late latent syphilis of more than two years duration) and after adequate treatment, or may be due to non venereal treponematoses.[17] We assume that in the present study most cases were in the late latent stage because the patients had been engaged in high risk sexual behaviour for a long time and might have contracted syphilis many years before. Early syphilis cases would have been detected at a follow-up visit and endemic syphilis is thought to be rare in Zaire now. Genital ulcers were only present in 7% of syphilis cases at enrolment compared with 4% of women with negative syphilis serology. Furthermore, syphilis patients more frequently had antibodies against *H ducreyi*. Positive *H ducreyi* serology was associated with a history of GUD in the previous five years, while positive syphilis serology was not, suggesting that more cases of GUD in the study population are caused by *H ducreyi* than *T pallidum*. However, the strongest argument for late latent stage is the evolution of RPR titres in HIV-negative patients after treatment. In the early stages of syphilis, the RPR titres should have declined more rapidly and in a higher proportion of patients.[18 19]

Among the HIV-negative women with low initial RPR titres in the present study we found a cumulative total of 30% seroreversals 12 months after treatment, and 40% 24 months after treatment. These figures are lower than those found in the treatment of early latent syphilis. In fact, they are also more consistent with the results of treatment of patients with late latent syphilis.[20] Furthermore, that study also demonstrated that patients with low initial RPR titres became seronegative sooner than patients with higher initial RPR titres.[20] Both observations are consistent with our data among HIV-negative syphilis patients, of whom only 44% of those with an initial RPR titre lower than 1:8 seroreversed.

The effect of HIV on the performance of serology for the diagnosis of syphilis remains controversial.[5 21] All reports have been on patients with early syphilis. Very little information is available on alterations of syphilis serology in HIV-positive patients with late latent syphilis. Dowell *et al* found that 88% of their patients with latent syphilis had an RPR titre greater than or equal to 1:16.[22] They argued that these were higher-than-expected titres because they were higher than the RPR titres observed in an earlier study among HIV-negative patients with late latent syphilis.[20] In our population, the RPR results among HIV-positive and HIV-negative patients with syphilis are more in line with the results obtained in Fiumara's study.[20] In both groups, low RPR titres were predominant, but HIV-positive patients had lower GMTs of RPR than the HIV-negative patients. The difference could not be attributed to factors such as differences in mean age, duration of prostitution or sexual exposure, since the two groups were comparable with regard to these variables.

Regardless of the pre-treatment RPR titre, the serological response to syphilis therapy (measured by evolution of RPR titres) was similar in HIV-positive and HIV-negative subjects. The probability of the RPR titre declining fourfold or more after the two year period was 83% in HIV-positive and 90% in HIV-negative patients with an initial RPR titre of 1:8 or more. However, since there were only six HIV-positive patients with high initial RPR titres, the 95% confidence intervals were very large and the results must therefore be interpreted with caution, especially since the stage of HIV disease of these women is not known and serological response may vary with stage of disease. It should also be noted that only 20% of HIV-negative and none of six HIV-positive patients with an initial RPR titre of 1:8 or more became RPR seronegative after two years.

The similar response to therapy observed among HIV-positive and HIV-negative women conforms to results obtained by some other investigators. In a study on the efficacy of syphilis therapy among HIV-positive and HIV-negative male intravenous drug users with different stages of syphilis in New York City, HIV infection did not alter the response to treatment. All 26 HIV-positive and 16 of 17 HIV-negative patients responded well to therapy.[23] In another study among 56 HIV-

positive and 274 HIV-negative patients with early syphilis, the serological response to treatment was similar in both groups and no clinical failures were observed.[24] However, in a case-control study in New York City, HIV-positive patients with primary syphilis showed a decreased serological response to therapy as compared to HIV-negative patients with primary syphilis. For patients with secondary syphilis this response was independent of the HIV-serostatus.[13]

In this study, patients received the therapy recommended by the CDC and the WHO for late syphilis (that is, late latent syphilis of more than two years' duration but otherwise of unknown duration, late benign syphilis), namely benzathine penicillin G, 2·4 million units intramuscular weekly for three consecutive weeks. We opted for this treatment schedule for all patients because the duration of the infection was unknown in virtually every patient. The efficacy of this treatment schedule among HIV-positive patients has been put in doubt in recent times. Neurosyphilis may be more frequent among HIV-positive syphilis patients even after receiving supposedly adequate penicillin therapy,[25-26] possibly because of the low concentrations of this antibiotic in the cerebrospinal fluid (CSF). However, in view of our results, and particularly in a developing world setting, the current recommended schedule with benzathine penicillin remains the most feasible option, because of its low cost and the ease of administration.

The results of this study confirm results from prior studies that syphilis serology (both RPR and TPHA) may be altered in HIV infection but suggests that the serological response to therapy is similar in both HIV-positive and HIV-negative patients.

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