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A Prospective Study of the Influence of HIV Status on the Seroreversion of Serological Tests for Syphilis

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Key Words

HIV infection · Syphilis · TPHA · VDRL test · FTA-Abs test

Abstract

The evolution of serological tests for syphilis (STSs) after therapy in HIV+ patients is a major point of controversy, with possible seroreactivation and illicit seroreversion in these patients. The aim of our study was to evaluate the long-term outcome of STSs in a cohort of HIV+ male homosexuals with a history of treated syphilis as compared with HIV– controls. ***Patients and Methods:*** Sixty-nine HIV+ male homosexuals with a documented history of treated syphilis and positive baseline treponemal tests were prospectively studied between 1986 and 1993. A medical examination, HIV staging, CD4+ cell count, VDRL, FTA-Abs tests and TPHA were performed every 6 months. Controls consisted of 49 HIV– patients with similar inclusion criteria over the same period. Comparisons between subgroups were based on χ^2 and Kruskal-Wallis tests. Analysis of negativation of the STS used the failure data methods (Kaplan-Meier, log-rank and Cox's model). ***Results:*** Patients had a mean age of 38 years, a baseline CD4+ cell count of 578/mm^3, elapsed time since last syphilis of 7.5 years and a median follow-up of 4.3 years. Controls had a mean age of 42 years, elapsed time since last syphilis of 5.3 years and a median follow-up of 4.7 years. Time to seroreversion was shorter in HIV+ patients for TPHA ($p = 0.009$, log-rank test) and FTA-Abs test ($p = 0.001$, log-rank test), even after adjustment for stage of syphilis, age and time since the last episode of syphilis. The decrease in VDRL titres was not different between the 2 groups ($p = 0.053$, log-rank test). Seroreversion of the TPHA, FTA-Abs test and VDRL test was not significantly related to stage of syphilis, time elapsed since the last episode of syphilis, age or history of STDs in both groups. Seroreversion of the TPHA and VDRL test was not related to baseline CD4+ cell count. However, seroreversion of the FTA-Abs test was related to a low baseline CD4+ cell count ($p = 0.003$). In HIV+ patients, a significant decrease in titres was noticed for TPHA, FTA-Abs test and VDRL test over time, but this time effect remained only for TPHA titres after adjustment for the CD4+ cell count. ***Conclusion:*** TPHA may serorevert in HIV+ patients. Thus, a non-reactive TPHA does not exclude a past syphilis infection in such patients. Evolution of the VDRL test after therapy is regular in HIV+ patients. The VDRL test remains adequate for controlling the efficacy of treatment in these patients.

Interrelations between syphilis and human immunodeficiency virus (HIV) infection are complex. Both are sexually transmitted diseases (STDs) [1]. Syphilis is a marker

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of a sexual risk behaviour. Its prevalence is higher in HIV-seropositive homosexuals when compared to HIV-seronegative homosexuals [2]. Moreover, genital ulcerations caused by syphilis or other STDs are strongly related to the acquisition of HIV infection both in homosexuals and heterosexuals, because of disruption of the mucosal barriers [3]. Some authors have stressed that syphilis was severer in HIV-seropositive patients, and cases of early severe neurosyphilis, ocular syphilis and profuse or atypical cutaneous involvement have been reported [4]. Several cases of secondary syphilis with negative serological tests for syphilis (STSs) have also been observed [5]. Bias of publication is likely and there is no evidence that the prevalence of severe or atypical syphilis is really higher in HIV-seropositive patients [6].

A major point of controversies is the evolution of STS in these patients. There are some conflicting theoretical arguments for both seroreactivation due to polyclonal non-specific activation of antibody production by HIV infection, and seroreversion or failure of specific antibody production because of immune suppression [7]. Interpretation of STS could also be hampered by the frequent positivity of anticardiolipin antibodies in these patients [8]. There are conflicting data in the reports of STS evolution after syphilis in HIV-seropositive patients [9–16].

The aim of our study was to assess the long-term outcome of STS in a cohort of HIV-seropositive male homosexuals with a history of syphilis compared with HIV-seronegative syphilitic controls.

Patients and Methods

Sixty-nine HIV-seropositive non-intravenous-drug user male homosexuals with a documented history of treated syphilis and positive baseline treponemal tests were prospectively studied during the period 1986–1993. These patients were followed at the STD clinic of the Hôpital Saint-Louis (Paris) with at least 3 follow-up visits. Positive treponemal tests were defined by a positive *Treponema pallidum* haemagglutination assay (TPHA) or a positive fluorescent treponemal antibody absorption test (FTA-Abs test) or both.

At the initial visit, a medical questionnaire was completed, pointing to the history of STDs and syphilis (stage, date and therapeutic regimen for the last documented episode). HIV staging was established according to the 1986 CDC criteria of HIV infection [17]. Every 6 months, a medical examination and laboratory tests including CD4+ cell count, the Venereal Disease Research Laboratory (VDRL cardiolipin antigen; Behring, Marburg, Germany) and treponemal tests (i.e. both TPHA – Bayer Diagnostics, Puteaux, France – and FTA-Abs test) were performed. Results of the TPHA were qualitatively assessed from negative (0) to 3+ (3). Results of the VDRL test were quantitatively assessed, the titre being given by the last dilution of serum giving positivity. Serum whose agglutination was observed only on non-diluted specimens was quoted 0.5 (for a ±, + or ++ agglutination) or 1 (for a +++ agglutination). Results of the FTA-Abs test were quantitatively assessed, the titre being given by the last dilution of serum giving positivity. At the time the study was begun, HIV viral load was not available.

Controls

Controls consisted in 49 HIV-seronegative male patients with positive baseline treponemal tests and a documented history of treated syphilis, followed for more than 6 months with at least 3 follow-up visits during the same period (1986–1993).

End-Points

The end-points were the time to seroreversion of the VDRL test, FTA-Abs test and TPHA when these had been positive at inclusion. The times were calculated from the date of inclusion into the study. In the absence of seroreversion, these times were censored at the date of the last available follow-up. Thus, the definition allows the use of failure time data methods.

Statistical Analysis

Comparisons for baseline characteristics between groups (either HIV-seropositive and HIV-seronegative patients, or stages of syphilis for both HIV status) were based on the χ^2 test for categorical variables or on the Kruskal-Wallis test for continuous variables. The analysis of seroreversion of VDRL, FTA-Abs tests and TPHA used the failure time data methods (Kaplan-Meier estimate [18], log-rank test [19] and proportional hazard Cox's model [20]). Failure time data were calculated from the date of entry into the study. In each HIV status group, stage of syphilis, age, time elapsed since the last documented syphilis and history of other STDs were assessed at baseline for the time to seroreversion of VDRL, FTA-Abs tests and TPHA using the log-rank test; in the HIV-seropositive patients, CD4+ cell count (<400 vs. $\geq 400/mm^3$ and <600 vs. $\geq 600/mm^3$) and CDC stage (I, II vs. IV) at baseline were also assessed for the end-points.

The time to seroreversion of STS was compared according to HIV status by the log-rank test and this comparison was adjusted according to baseline characteristics by the Cox's model. Given the imbalances between HIV-seropositive and HIV-seronegative patients and the predictive value in both groups, the adjustment model included age, time since the last episode of syphilis and stage of syphilis for all end-points. Thereafter, the biological data collected during follow-up (STS in HIV-seropositive and HIV-seronegative patients and CD4+ cell count in HIV-seropositive patients) were analysed for assessing a time trend using the general linear model. Levels of significance were represented by p values derived from two-sided tests; a p value less than 0.05 was considered to indicate statistical significance. The SAS software (Statistical analysis Software, Carey, N.C., USA) was used.

Results

HIV-Seropositive Patients

Data concerning the 69 HIV-seropositive patients are shown in table 1. All of them had a documented history of syphilis (primary, secondary or latent) before entry in the study, with a median elapsed time of 7.5 years between the last episode of syphilis and the study. All patients had

Table 1. Baseline characteristics and follow-up in 69 HIV+ patients

Stage of syphilis	Primary syphilis (n = 17)	Secondary syphilis (n = 33)	Latent syphilis (n = 19)	All (n = 69)	p value
Median age, years	40	35	39	38	0.45[a]
History of STD other than syphilis, n	10 (59)	21 (64)	11 (58)	42 (61)	0.81[b]
CDC staging, n					
II	13 (76)	25 (76)	13 (68)	51 (74)	0.81[b]
III	4 (24)	7 (21)	5 (26)	16 (23)	
IV C1	–	–	–	–	
IV C2	–	–	1 (5)	1 (1)	
IV D	–	1 (3)	–	1 (1)	
Median CD4 count, n/mm^3	547	660	556	578	0.70[a]
Median elapsed time since last documented treated, syphilis, years	7	7	9.1	7.5	0.21[a]
VDRL titre, n					
0	6	8	6	20	
0.5	7	9	12	28	
1	2	5	0	7	
2	0	0	1	1	
≥4	2	11	0	13	
Median	0.5	0.5	0.5	0.5	0.047[a]
FTA-Abs test titre, n					
0	5	5	5	15	
10–80	3	4	2	9	
100	5	7	8	20	
200	2	3	1	6	
≥400	2	14	3	19	
Median	100	200	100	100	0.04[a]
TPHA titre, n					
1	1	1	0	2	
2	2	4	3	9	
3	14	28	16	58	
Median	3	3	3	3	0.96[a]
Median follow-up, years	3.4	4.5	4.2	4.3	0.43[a]

Figures in parentheses indicate percentages.

[a] Kruskall-Wallis test.

[b] χ^2 test.

been adequately treated with benzathine penicillin or benethamine penicillin.

Most of the patients (97%) were asymptomatic or had lymphadenopathy at entry in the study. The median CD4+ cell count was 578/mm^3. Sixty-one percent had a history of STDs other than syphilis (including genital herpes, urethritis and genital warts). The median VDRL test at entry was 0.5, the median FTA-Abs test 100 and the median TPHA 3. The median follow-up was 4.3 years.

At the end of the follow-up, the median CD4+ cell count was 139/mm^3, 20 patients had had major opportunistic infections, 7 minor opportunistic infections, 4 Kaposi's sarcoma and 17 died during the study. Median VDRL, FTA-Abs tests and TPHA were 0, 20 and 3, respectively. Although the median values were not different, differences according to the stage of syphilis were found in the distribution of the baseline VDRL result ($p = 0.047$; $p = 0.02$ when comparing secondary vs. latent syphilis) and FTA-Abs test ($p = 0.04$; $p = 0.04$ when comparing secondary vs. both primary and latent syphilis). According to the stage of syphilis, no difference was found in the distribution of age, history of STDs, baseline CDC stage, baseline CD4+ cell count, elapsed time since the last documented treated syphilis, length of follow-up and baseline TPHA.

Table 2. Baseline characteristics and follow-up in 49 HIV– patients

Stage of syphilis	Primary syphilis (n = 25)	Secondary syphilis (n = 11)	Latent syphilis (n = 13)	All (n = 49)	p value
Median age, years	38	43	46	42	0.38[a]
History of STD other than syphilis, n	13 (52)	5 (45)	5 (38)	23 (47)	0.73[b]
Median elapsed time since last documented treated syphilis, years	4.8	6.1	5.3	5.3	0.78[a]
VDRL titre, n					
0	11	5	4	20	
0.5	9	4	5	18	
1	3	2	3	8	
2	1	0	1	2	
≥4	1	0	0	1	
Median	0.5	0	0.5	0.5	0.03[a]
FTA-Abs test titre, n					
0	6	3	1	10	
10–80	6	3	4	13	
100	5	3	3	11	
200	4	2	3	9	
≥400	4	0	2	6	
Median	100	20	100	100	0.36[a]
TPHA titre, n					
1	2	0	0	2	
2	3	0	1	4	
3	20	11	12	43	
Median	3	3	3	3	0.10[a]
Median follow-up, years	4.7	5.6	4.4	4.7	0.50[a]

Figures in parentheses indicate percentages.

[a] Kruskall-Wallis test.

[b] χ^2 test.

Controls

Data concerning the 49 HIV-seronegative patients are shown in table 2. All had a documented history of treated syphilis with a median of 5.3 years before entry in the study. The median follow-up was 4.7 years. Differences according to the stage of syphilis were found in the distribution of the VDRL results (p = 0.03) but not in the other variables. Comparisons of baseline characteristics of HIV-seropositive and HIV-seronegative patients appear in table 3, HIV-seronegative patients being slightly older (p = 0.04), HIV-seropositive patients having had more STDs other than syphilis (p = 0.02) and HIV-seropositive patients having had secondary syphilis more often (p = 0.005).

Comparison of Time to Negativation of STS according to HIV Status

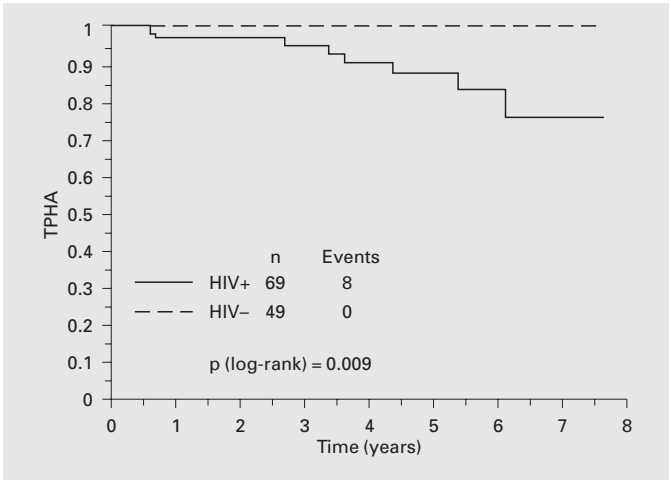
Time to seroreversion was studied in patients with a positive baseline test (HIV-seropositive patients: TPHA n = 69, FTA-Abs test n = 54, VDRL test n = 49; HIV-seronegative patients: TPHA n = 49, FTA-Abs test n = 39, VDRL test n = 29). Comparisons between HIV-seropositive and HIV-seronegative patients appear in figures 1–3.

Seroreversion of the TPHA was significantly more frequent in HIV-seropositive patients (log-rank test, p = 0.009). Because none of the HIV-seronegative patients had seroreversion of TPHA during the study, no adjustment by Cox's model was possible for numerical reasons according to the stage of syphilis, time since the last episode of syphilis and age.

Seroreversion of the FTA-Abs test was significantly more frequent in HIV-seropositive patients either by the log-rank test (p = 0.001) or after adjustment for the stage of syphilis, time since the last episode of syphilis and age (Cox's model, p = 0.001).

Seroreversion of the VDRL test was not statistically different between HIV-seropositive and HIV-seronegative patients (log-rank test, p = 0.053, Cox's model, p = 0.17).

Seroreversion of TPHA, FTA-Abs and VDRL tests was not related to stage of syphilis, time elapsed since the last



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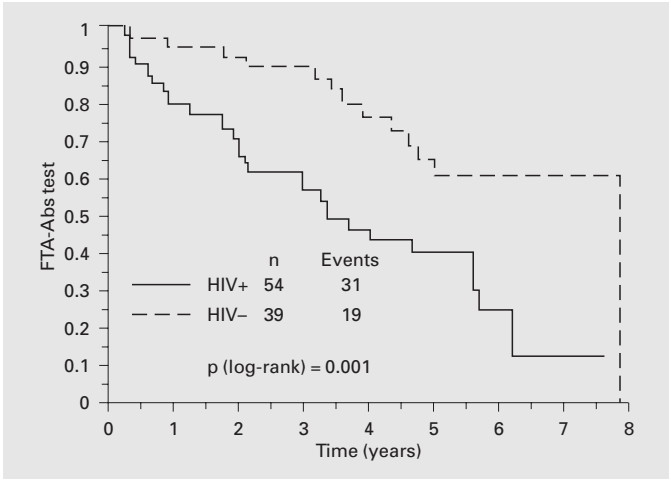

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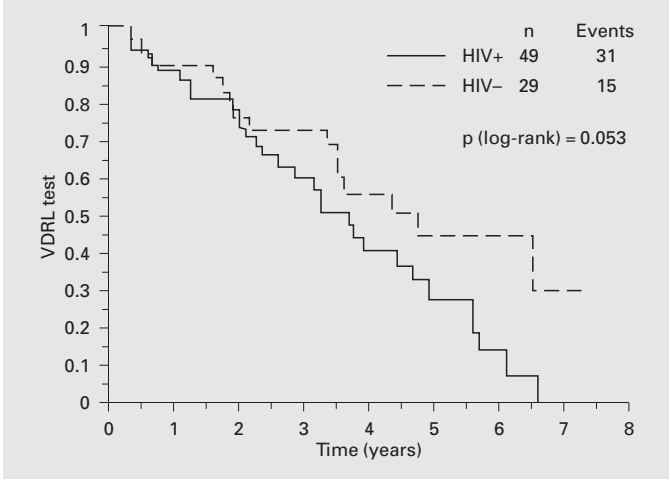

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Fig. 1. Time to negativation of the TPHA in patients with a positive TPHA at baseline according to HIV status.

Fig. 2. Time to negativation of the FTA-Abs test in patients with a positive FTA-Abs test at baseline according to HIV status.

Fig. 3. Time to negativation of the VDRL test in patients with a positive VDRL test at baseline according to HIV status.

Table 3. Baseline characteristics in HIV+ patients (n = 69) and controls (n = 49)

Group	HIV+ patients (n = 69)	HIV– patients (n = 49)	p value
Age, years	38	42	0.04[a]
History of STD other than syphilis, n	42 (61)	23 (47)	0.02[b]
Median elapsed time since last documented treated syphilis, n	7.5	5.3	0.10[a]
Stage of syphilis, n			
Primary	17 (25)	25 (51)	0.005[b]
Secondary	33 (48)	11 (22)	
Latent	19 (27)	13 (27)	
VDRL titre, n			
0	20	20	
0.5	28	18	
1	7	8	
2	1	2	
≥4	13	1	
Median	0.5	0.5	0.09[a]
FTA-Abs test titre, n			
0	15	10	
10–80	9	13	
100	20	11	
200	6	9	
≥400	19	6	
Median	100	100	0.21[a]
TPHA titre, n			
1	2	2	
2	9	4	
3	58	43	
Median	3	3	0.92[a]
Median follow-up, years	4.3	4.7	0.09[a]

Figures in parentheses indicate percentages.
[a] Kruskall-Wallis test.
[b] χ^2 test.

episode of syphilis, age or history of STDs in both groups. In HIV-seropositive patients, seroreversion of STS was not related to baseline CDC stage. Seroreversion of the TPHA and VDRL test was not related to baseline CD4+ cell count. However, seroreversion of the FTA-Abs test was significantly more frequent in patients with low baseline CD4+ cell count (p = 0.003).

In HIV-seronegative patients, the analysis of STS over time showed no time effect for the FTA-Abs test (p = 0.38) and VDRL test (p = 0.12) but a significant decrease over time for the TPHA (p = 0.02). In HIV-seropositive patients, all STSs showed a significant decrease over time (TPHA,

p = 0.0001, FTA-Abs test, p = 0.0006, VDRL test, p = 0.01). When the model included the CD4+ cell count over time, only a significant decrease was observed for the TPHA (p = 0.0001), underlining the effect of immune suppression on FTA-Abs and VDRL titres.

Only 3 patients, all HIV-seropositive, had an increase in their STS titres during the study with no evidence of reinfection. In all 3 cases, a cerebrospinal fluid examination was performed and found to be normal. All 3 had CD4+ cell counts lower than 100/mm^3. All these 3 patients were retreated.

Discussion

There are conflicting results in the reports of STS evolution after syphilis in HIV-seropositive patients [6, 7, 9–16, 21]. These discrepancies point to the difficulties of obtaining a control group, which is absent in most of the studies, and to the still-existing controversies in the long-term follow-up of STS in HIV-seronegative patients. Titres of the treponemal and non-treponemal tests are related to the stage of syphilis, the duration since the last episode of syphilis (which may be well documented or not) and the existence of a history of treated syphilis before a new episode. Most of the studies of STS kinetics in HIV-seronegative patients concern early syphilis in naive patients, use non-treponemal tests and have a short follow-up.

Follow-up of STS in HIV-Seronegative Patients

It has long been stated that non-treponemal tests such as the VDRL and the rapid plasma reagin (RPR)-CT were rapidly decreasing after treatment of early syphilis. Titres should demonstrate a fourfold drop at 6 months [22] and become negative at 1 year for primary syphilis, 2 years for secondary syphilis and 4 years for early latent syphilis [23, 24]. Patients who do not fulfil these criteria are considered as therapeutic failures on disputable grounds and are excluded from the studies with a risk of circular reasoning [23, 24]. In fact, in many series, non-treponemal tests are far from serorevert in such a rapid way. Negativation of the VDRL test could occur in 72–97% of patients 2–3 years after treatment of primary syphilis [25–29], in 56–92% of patients 2–5 years after treatment of secondary syphilis [25–30] and in 81–88% of patients 3–5 years after treatment of early latent syphilis [27, 30]. Seroreversion of non-treponemal tests in late latent syphilis is mostly unknown just as the long-term evolution of the VDRL test after remaining positive after 2–5 years. Our conviction is that titres continue to decrease and can serorevert after very long periods.

The state of the art concerning treponemal tests is still more difficult to establish. As soon as they are positive, TPHA, FTA-Abs test and microhemagglutination assay (MHA-TP) are said to remain positive indefinitely after adequate treatment, even in early syphilis [31]. Nevertheless, Schroeter et al. [26] reported a 10% seroreversion of the FTA-Abs test 1 year after primary syphilis, Thivolet et al. [30] a 68% seroreversion of the FTA-Abs test 3 years after primary syphilis and an 18% seroreversion after secondary syphilis and Romanowski et al. [28] a 24% seroreversion of the FTA-Abs test and a 13% seroreversion of the MHA-TP 3 years after primary syphilis. Schroeter et al. [26] and Romanowski et al. [28] did not report any seroreversion of the treponemal tests in secondary syphilis, but their follow-up was short. It is possible that the FTA-Abs test and MHA-TP or TPHA can serorevert after very long periods in primary and secondary syphilis. No data exist on late syphilis, treponemal tests being thought to remain indefinitely positive after adequate treatment.

Follow-Up of STS in HIV-Seropositive Patients

Few data exist on the evolution of STS after treatment of HIV-seropositive patients, only 4 major studies having been published in the last 6 years [11, 14–16]. In the first, Haas et al. [15] reported that treponemal tests (MHA-TP or FTA-Abs test) seroreverted in 13 (7 MHA-TP and 6 FTA-Abs test) out of 90 HIV-seropositive but in none out of 19 HIV-seronegative male homosexuals. The mean duration between the last episode of documented syphilis and the study ranged from 50 to 106 months. Low CD4+ cell count, symptomatic HIV infection, single prior episode of syphilis and VDRL <32 during the last episode of syphilis were independent predictors of seroreversion. The geometric mean VDRL on enrolment was non-reactive, but no other data were given concerning the VDRL. The authors concluded that loss of reactivity was related to immune function and not to duration since syphilis infection. Although this study was retrospective and made on only one serum, it brings consistent information on the loss of treponemal test reactivity in HIV-seropositive patients. No specific discrimination was made between MHA-TP and FTA-Abs test [15]. Similar trends were found by Johnson et al. [14]. In their study, seroreversion of both TPHA and FTA-Abs test occurred in 3/29 AIDS patients but in none of 29 controls. The difference was not statistically significant. Their study was retrospective and based on 2 sera at a 3-year interval. The authors concluded that non-reactive STSs do not exclude a past syphilis infection in patients with AIDS [14]. The prospective study by Gourevitch et al. [11] compared 26 HIV-seropositive and 17 HIV-seronegative intravenous-

drug addicts followed for 1 year after treatment of syphilis (mostly latent). The VDRL test was consistently higher in HIV-seropositive patients. No difference was found in seroreversion of treponemal tests (FTA-Abs test and/or MHA-TP) between the 2 groups (4/26 vs. 3/17). Loss of reactivity of the treponemal tests was unrelated to the stage of syphilis, CD4+ cell count or history of syphilis but was weakly associated with a low non-treponemal titre. The decrease in non-treponemal titres was not different in HIV-seropositive and HIV-seronegative patients but was slightly slower in more advanced stages of syphilis [11]. These findings are discrepant with those of Haas et al. [15] and Johnson et al. [14], but the number of patients studied was small and the follow-up was short. Moreover, STS seroreversion could be different in intravenous-drug addicts as compared to male homosexuals. Finally, Rolfs et al. [16], comparing 69 HIV-infected and 257 not HIV-infected patients with various stages of early syphilis found that HIV-infected patients were more likely than patients without HIV infection to have higher titres of the RPR test and serologically defined treatment failure at 6 months (observed only in primary syphilis).

Our study is prospective, with a longer follow-up (4.3 and 4.7 years) and thorough evaluation of both TPHA and FTA-Abs test. We found that seroreversion of TPHA was observed only in HIV-seropositive patients (8/69) and in none of the controls. Loss of reactivity was not related to the stage of syphilis, age, time elapsed since the last episode of syphilis, baseline CD4+ cell count or CDC staging. Seroreversion of the FTA-Abs test was observed in both groups and was associated with a low baseline CD4+ cell count in HIV-seropositive patients. Falls in the titres of the FTA-Abs test were more rapid in HIV-seropositive patients. Seroreversion of the VDRL test was also observed in both groups with a similar decline of titres. In HIV-seronegative patients, a significant time effect was found only for the TPHA. In HIV-seropositive patients, a time effect was found for all tests but remained significant only for TPHA titres after adjustment for the CD4+ cell count, stressing the importance of the effect of the CD4+ cell count on VDRL and FTA-Abs test titres.

Discrepancies between the 5 major studies [11, 14–16, ours] could be only apparent. The main point is that the TPHA can revert in HIV-seropositive patients whereas seroreversion is never or very rarely observed in HIV-seronegative patients (Gourevitch et al. [11] do not indicate which test – MHA-TP or FTA-Abs test – have seroreverted in their 3 HIV-seronegative patients who had seroreversion of their treponemal tests). As far as the FTA-Abs test is concerned, it is well known that this test has a more rapid decrease after treatment than the TPHA and can serorevert in HIV-seronegative patients [26, 28, 30]. The reason why Haas et al. [15] and Johnson et al. [14] did not find seroreversion of the FTA-Abs test in HIV-seronegative patients could be due to a short follow-up. Finally, the higher titres of the RPR test in the HIV-seropositive patients studied by Rolfs et al. [16] are observed only in primary syphilis after a short follow-up and the evolution of non-treponemal tests appears similar in HIV-seropositive and HIV-seronegative patients in both the study of Gourevitch et al. [11] and ours. This statement is very important, non-treponemal test titres being classically used for controlling the efficacy of treatment [22]. Thus, no specific recommendation appears necessary in HIV-seropositive patients.

The reasons for which treponemal tests decline more rapidly in HIV-seropositive patients are not clear. Immune dysfunction is complex in these patients. Treponemal test seroreversion is not clearly related to the importance of the immune deficiency, some authors finding a relation [15], others not [11]. We only found a correlation with low CD4+ cell numbers (baseline and over time) for the FTA-Abs test and not for the TPHA.

Seroreversion of the TPHA seems to be a very particular finding in HIV-seropositive patients. Thus, a non-reactive TPHA does not exclude a past syphilis infection in such patients. This could nevertheless be of no importance if they are cured. In the study of Rolfs et al. [16], detection of *T. pallidum* in cerebrospinal fluid after treatment was no more common in HIV-infected patients, although the serological response was different.

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