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ORIGINAL RESEARCH

Consider Syphilis in Case of Lymphopenia in HIV-Infected Men Who Have Sex with Men (MSM): A Single-center, Retrospective Study

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ABSTRACT

Introduction: The way syphilis affects the immunologic and virologic parameters of a human immunodeficiency virus (HIV) infection remains controversial. The aim of this study was to investigate the impact of syphilis infection on lymphocyte and lymphocyte subset counts as well as viral load in HIV-infected patients.

Methods: All HIV-infected patients attending the outpatient clinic for infectious diseases of Hannover Medical University Hospital diagnosed with syphilis between 2009 and 2016 were retrospectively evaluated for changes in total lymphocyte, B cell, $CD3^+$ T cell, $CD4^+$ and $CD8^+$ T cell counts as well as in HIV viral load. These parameters were assessed at three different time points, i.e., 3–6 months before, at diagnosis and 3–6 months after treatment of syphilis.

Results: Eighty-four HIV-infected patients, all with early syphilis, were identified. The vast majority were men who have sex with men (MSM), and 80% were receiving antiretroviral therapy (ART). Syphilis was associated with a significant reduction in the total lymphocyte count and counts of all studied lymphocyte subsets, including $CD4^+$ T cells, whose percentage among lymphocytes did not change. No significant changes in HIV viral load were observed at any of the studied time points. Further, antibiotic treatment of syphilis restored lymphocyte counts back to pretreatment levels.

Conclusion: Syphilis induces a relative non-$CD4^+$ T cell-specific lymphopenia in HIV-infected patients. Our data suggest that serologic testing for syphilis should be considered in HIV-infected MSM in case of an otherwise unexplained drop in total lymphocyte count.

Keywords: B cells; CD4 cell count; CD8 cell count; HIV; Men who have sex with men; Sexually transmitted disease; Syphilis; Viral load

Georgios Sogkas and Diana Ernst contributed equally to the manuscript.

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INTRODUCTION

Syphilis and HIV coinfection is common, as both of these infectious diseases are similarly transmitted and hence affect patients with similar risk behaviors [1–3]. The incidence of syphilis is especially high and appears to be increasing in Europe among men who have sex with men (MSM) [4]. Further, in Europe, approximately two-thirds (63%) of new cases of syphilis were reported among this high-risk population [4].

Immunologic interactions between syphilis and HIV infection are complex. HIV infection-associated immunodeficiency may affect the course of syphilis by resulting in increased spirochetal proliferation and syphilis progression to late disease stages [5, 6]. Syphilis appears to enhance transmission of HIV not only through the high incidence of genital ulcers, but also through the immunomodulatory effects of *Treponema pallidum* [3, 7]. Furthermore, it has been postulated that enhanced immune activation as a consequence of syphilis may affect the course of an existing HIV infection [8, 9]. The effect of syphilis on the immunologic and virologic parameters of a concurrent infection with HIV has been debated, although the majority of published studies have described a drop in the $CD4^+$ T cell count with a concomitant increase in HIV viral load during syphilis [10–12].

Here we aim at evaluating the effect of syphilis on total lymphocyte count and B cell, $CD3^+$ T cell, $CD4^+$ and $CD8^+$ T cell counts as well as in HIV viral load. We therefore retrospectively assessed the impact of newly diagnosed syphilis on the aforementioned parameters before, at diagnosis and after treatment of syphilis.

METHODS

Data Collection

This single-center retrospective study included all new cases of syphilis among HIV-positive patients diagnosed between 1 January 2009 and 31 December 2016 in the outpatient clinic for infectious diseases of Hannover Medical University. We identified 101 HIV-positive patients with new syphilis infection (Fig. 1a). Seven patients were excluded because of lack of date for the studied time points. To eliminate the influence of antiretroviral therapy (ART) on the evaluated parameters, ten patients who started or changed ART within or 6 months before the studied period around the diagnosis of syphilis were excluded from this study. Visits of HIV-infected patients were scheduled approximately every 3 months. Serologic screening for syphilis was performed routinely every 3–6 months in HIV-infected MSM patients and every 9–12 months in non-MSM HIV-infected patients. Immunologic parameters, including $CD4^+$ T cell count and HIV-RNA viral load, were regularly measured every 3 months as suggested by the German-Austrian guidelines [13]. Seven additional patients were excluded from this study because of lack of required data (i.e., cell counts and/or viral load) for the study period. Diagnosis of syphilis was based on serologic testing, which was performed at the Institute of Medical Microbiology of Hannover Medical University. Initial screening included a treponemal test [*Treponema pallidum* particle agglutination (TPPA) test], and, in case of positivity, confirmatory tests, i.e., immunoblot testing for *Treponema pallidum*-specific IgG and IgM antibodies and/or a non-treponemal test (cardiolipin-complement fixation test), were performed. Irrespective of the

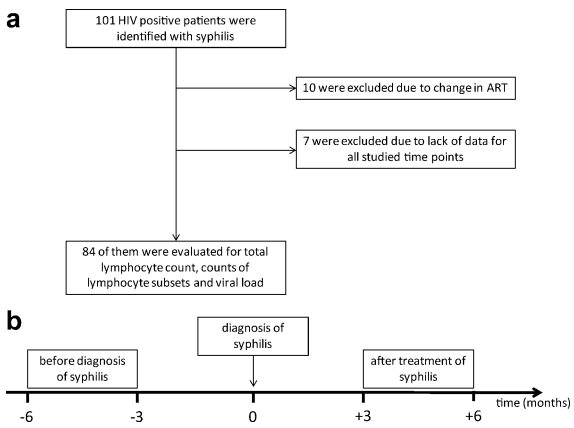

Fig. 1 Study design. **a** Retrospectively identified patients and studied patients. **b** Time points studied

clinical staging of syphilis, all HIV-positive patients diagnosed with syphilis were admitted to our hospital for intravenous treatment with penicillin G (24 million IU per day) or ceftriaxone (2 g per day), in case of allergy to penicillin, for 14–21 days, as if they had neurosyphilis. All patients completed an at least 14-day-long antibiotic regimen, which was well tolerated. In a patient with documented severe beta-lactam antibiotic allergy, penicillin was administered after desensitization [14]. Mean duration of the antibiotic regimen was 14.38 days. Counts of peripheral blood lymphocyte subsets and HIV-RNA PCR were performed in the HIV laboratory of Hannover Medical University.

Statistical Analysis

Data analysis was performed with GraphPad 5 software. Cell counts and viral load before (3–-6 months before) diagnosis of syphilis, during (at the time point of diagnosis, before antibiotic treatment) and after treatment of syphilis (3–-6 months after antibiotic treatment) were compared using a paired *t* test (Fig. 1b). Changes in cell counts during syphilis were evaluated by subtracting values during diagnosis from values before diagnosis and by subtracting values after treatment from values during syphilis. In all statistical analyses P values < 0.05 were considered significant. The study was performed in compliance with national policies, the policies of the ethics committee of Hannover Medical University and the 1964 Helsinki Declaration and its later amendments.

RESULTS

We identified 84 HIV-positive patients with early syphilis who fulfilled the above-discussed inclusion criteria. In 16 patients (19%) neurosyphilis was diagnosed according to the German guidelines for diagnosis and therapy of syphilis [15]. Nine patients were diagnosed with probable neurosyphilis on the basis of serologic findings and ocular or neuropsychiatric manifestations, which resolved after antibiotic treatment. In seven patients a certain cerebrospinal fluid-based diagnosis of neurosyphilis was made; this number, however, may underestimate the incidence of certain kinds of neurosyphilis in this cohort, as lumbar puncture was not performed in all patients with suspected neurosyphilis because of the above-described antibiotic treatment. All but one patient were male. For 65 of the 84 patients, an unambiguous risk factor for HIV infection could be identified. The vast majority of them (i.e., 56 of 65 with a documented unambiguous risk factor for HIV infection) were MSM. Sixty-seven patients (80%) were already on antiretroviral therapy (ART). Syphilis was diagnosed on average 6 years after diagnosis of HIV infection. Characteristics of the studied patients are summarized in Table 1.

Variations in total lymphocyte count, $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, B cells as well as percentage of $CD4^+$ T cells among lymphocytes 3–6 months before diagnosis of syphilis, at time point of diagnosis and 3–6 months after antibiotic treatment of syphilis are depicted in Fig. 2. We observed a significant reduction in total lymphocyte count and absolute counts of all studied lymphocyte subsets during syphilis, except for $CD8^+$ T cells. However, $CD8^+$ T cell counts increased significantly after antibiotic treatment. A decrease in the $CD4^+$ T cell count at diagnosis of syphilis compared with the $CD4^+$ T cell count either before diagnosis or after treatment of syphilis was observed in 78 out of 84 patients (92.9%). When comparing $CD4^+$ T cell counts before diagnosis and during syphilis, the mean change was a reduction by 77 cells/μl (interquartile range, IQR: − 160, 22). When comparing the $CD4^+$ T cell count after treatment and during syphilis, the mean change was 110 cells/μl (IQR: 174, 19). A decrease in absolute counts of $CD4^+$ T cells during syphilis did not match a reduction in their percentage among lymphocytes (mean change during vs. after − 0.48%, IQR: − 3, + 2, $P = 0.4654$, and mean change during vs. before − 0.33%, IQR: − 3, + 2, $P = 0.3025$). Considering the aforementioned and significant decrease in counts of all measured lymphocyte subsets during syphilis, a reduction in $CD4^+$ T cells appears to be the consequence of a non-subset-specific decrease in lymphocyte count. A separate study of the 67

Table 1 Characteristics of 84 HIV-positive patients at diagnosis of syphilis

Variable	*N* (%)/mean (IQR)
Male gender	83 (98.8)
Age (years)	44.6 (36–51.8)
Risk factor documented	65 (77.4)
MSM (% among patients documented risk factors)	56 (86.2)
Intravenous drug use (% among patients documented risk factors)	5 (7.7)
Heterosexual contacts (% among patients documented risk factors)	4 (6.2)
Time (years) since diagnosis of HIV infection	6 (1–9)
Patients with a history of an AIDS-defining disease	17 (20)
$CD4^+$ T cell counts	496 (329–617)
Viral load < 50 copies HIV-RNA/ml	64 (76.2)
Patients on ART	67 (80)
Viral load > 50 copies HIV-RNA/ml among patients on ART	3 (4.5)
Antibiotic regimen	
Penicillin G	53 (63.1)
Ceftriaxon	31 (36.9)

patients on ART and the rest of the patients without ART yielded similar results (Table 2). However, comparisons during and before diagnosis of syphilis in patients without ART were not significant, probably because of the limited number of patients. The 67 patients on ART were treated with two different nucleoside reverse transcriptase inhibitors (NRTIs) and a third antiretroviral of another class (an integrase inhibitor, protease inhibitor or non-nucleoside reverse transcriptase inhibitor). During the studied years (i.e., 2009–2016), the following three new antiretrovirals were introduced in our cohort: the integrase inhibitor dolutegravir available as a single drug ($n = 8$) or in fixed combination with the NRTIs abacavir and lamivudine ($n = 3$), the NNRTI rilpivirin, which in our cohort appears as a combination drug with emtricitabin and tenofovir disoproxil ($n = 3$), and elvitegravir, which in our cohort appears as a combination drug with cobicistat, emtricitabine and tenofovir disoproxil ($n = 1$ patient). Separate analysis of patients on ART regimens including the above-mentioned newer antiretrovirals and in particular dolutegravir and rilpivirin reveals similar changes in $CD4^+$ T cell and lymphocyte counts (Suppl. Table 1), suggesting that the above-mentioned newer antiretrovirals are unlikely to affect changes in total lymphocyte and lymphocyte subset counts in syphilis-infected HIV-positive patients, although—especially for rilpivirin and elvitegravir—it is difficult to judge because of the low number of patients.

No significant changes in HIV viral load were observed during syphilis (Fig. 3). Only nine (10.7%) of the studied patients exhibited an increase in HIV viral load during syphilis infection compared with the viral load values either before diagnosis of syphilis or after treatment of syphilis. Among patients on ART, two (3%) presented an increased viral load at diagnosis of syphilis compared with either before diagnosis or after treatment of syphilis. Increases in viral load were more frequent among patients without ART, with five patients

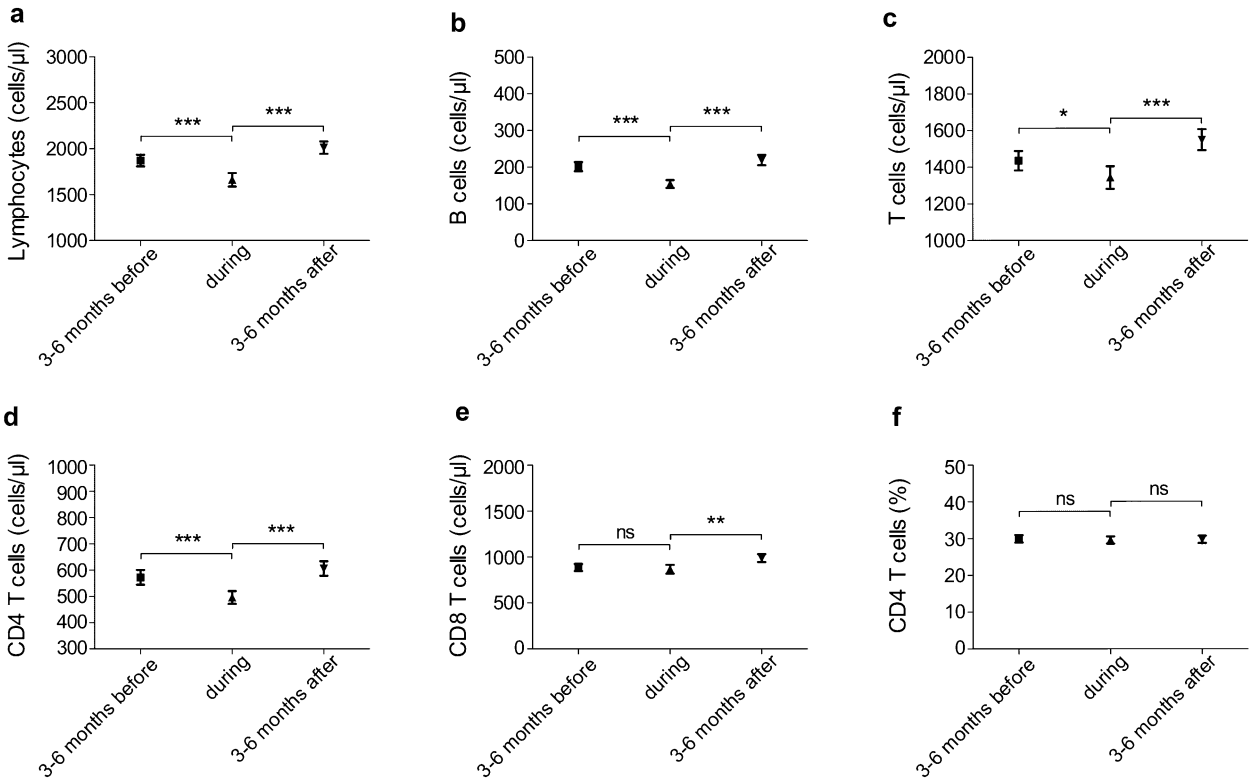

Fig. 2 Lymphocyte (**a**) and lymphocyte subset counts (**b**–**e**) as well as percentage of $CD4^+$ T cells among lymphocytes (**f**) before diagnosis of syphilis, at time point of diagnosis of syphilis and after treatment of syphilis at the indicated time points. Mean ± SEM values are depicted ($^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; ns: not significant)

(29.4%) presenting increased viral load at diagnosis of syphilis compared with either before diagnosis or after treatment of syphilis.

Of the 84 studied patients, we identified 7 who presented with reinfection with syphilis within the studied period and at least 1 year after antibiotic treatment and serologic cure of syphilis (defined as a negative cardiolipin-complement fixation test or an at least fourfold titer decrease 6 months after antibiotic treatment). For the six for whom data were available, a similar evaluation of lymphocyte counts could be performed (see Suppl. Table 2). Four of these patients exhibited a decrease in total lymphocyte counts, which was reversible after antibiotic treatment of syphilis (mean change during vs. after − 730, IQR: − 900, − 513 and mean change during vs. before − 141, IQR: − 350, 103). Five exhibited a decrease in $CD4^+$ T cell count, which was similarly reversible after antibiotic treatment of syphilis (mean change during vs. after − 233, IQR: − 333, − 115 and mean change during vs. before − 76, IQR: − 141, 15). Percentages of $CD4^+$ T cells among lymphocytes remained unaffected. All were on ART, and none presented a viral load above the detection level 3 months before and after or during reinfection. Thus, reinfection with syphilis appears to have the same impact on HIV-infection parameters, inducing a transient non-$CD4^+$ T cell-specific lymphopenia and no increase in viral load.

DISCUSSION

In this retrospective study, consistent with previous reports [10, 16, 17], syphilis infection in HIV-positive patients was associated with a

Table 2 Change in lymphocytes and lymphocyte subsets in HIV and syphilis-coinfected patients on ART (A) and those who did not start an ART (B)

	Before	During	After	During vs. before	During vs. after
(A) Patients on ART (n = 67)					
Lymphocytes	1853 (1450, 2081)	1628 (1260, 1920)	1986 (1665, 2432)	< 0.001***	< 0.001***
T cells	1385 (1002, 1708)	1293 (1015, 1575)	1491 (1056, 1856)	0.0432*	< 0.001***
CD4 T cells	590 (391, 830)	500 (317, 640)	620 (403, 759)	< 0.001***	< 0.001***
CD4%	31.2 (24, 37)	30.6 (24, 38)	31.2 (25, 38)	0.2392 (ns)	0.2591 (ns)
CD8 T cells	828 (620, 1028)	830 (495, 965)	931 (704, 1169)	0.9681 (ns)	0.0220*
B cells	210 (119, 286)	164 (95, 195)	229 (113, 312)	< 0.001***	< 0.001***
(B) Patients without ART (n = 17)					
Lymphocytes	1941 (1408, 2360)	1795 (1386, 2312)	2113 (1849, 2480)	0.1270 (ns)	0.0092**
T cells	1638 (1112, 2172)	1541 (1186, 1926)	1781 (1621, 2178)	0.2116 (ns)	0.0046**
CD4 T cells	502 (396, 584)	475 (349, 586)	550 (327, 681)	0.2234 (ns)	0.0210*
CD4%	24.8 (19.5, 31.5)	25.6 (23, 30)	25.7 (19, 33)	0.4282 (ns)	0.9223 (ns)
CD8 T cells	1117 (639, 1758)	1013 (766, 1382)	1216 (994, 1530)	0.1439 (ns)	0.0027**
B cells	168 (81, 225)	113 (78, 154)	179 (74, 277)	0.0207*	0.0061**

Mean ± IQR values are depicted
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ns: not significant

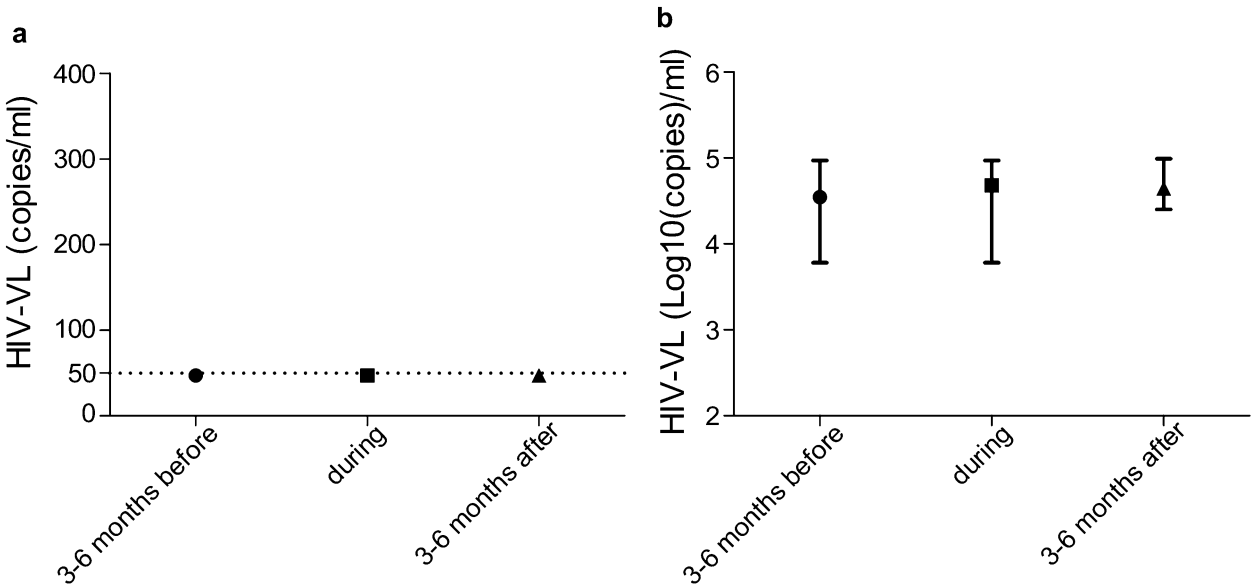

Fig. 3 HIV viral load (HIV-VL). **a** Patients on antiretroviral therapy (dashed line indicates the detection cutoff level of 50 HIV-RNA copies/ml) and **b** patients without ART (**c**). Median ± IQR values are depicted

significant reduction in $CD4^+$ T cell count. However, this change in $CD4^+$ T cells was not accompanied by a reduction in their percentage among lymphocytes. Further, total lymphocytes as well as counts of other lymphocyte subsets were also significantly reduced during syphilis. Thus, reduction in $CD4^+$ T cell counts appears to be a consequence of a non-subset-specific lymphopenia and not a specific depletion of $CD4^+$ T cells, which is the hallmark of progression of HIV infection [18]. It is however noteworthy that a decrease in $CD8^+$ T cells at diagnosis of syphilis compared with $CD8^+$ T cell counts before diagnosis remained non-significant. This may be explained through the relatively small number of patients evaluated in the present study. Alternatively, considering the significant increase in $CD8^+$ T cells after antibiotic treatment of syphilis, it is tempting to speculate that $CD8^+$ T cell counts may have decreased already before seroconversion.

Regarding viral load values, only a few syphilis-infected HIV-positive patients exhibited an increase during syphilis. Increases in viral load were considerably more common among patients without ART. However, there was no significant increase in viral load during syphilis compared with values before diagnosis and after treatment of syphilis in both ART-treated and untreated patients. Taken together, the aforementioned findings suggest that syphilis is not likely to affect the course of an HIV infection, especially in patients on ART. Reduction in lymphocyte and $CD4^+$ T cell counts during syphilis was reversible after antibiotic treatment and could reflect a sequestration of lymphocytes in spirochetal lesions [19, 20]. Several studies published before the discovery of HIV have described lymphocyte sequestration in spirochetal lesions in both humans and rabbits, which may explain the relative lymphopenia as a consequence of syphilis [21].

Although our finding on the unchanged viral load during syphilis contradicts some previous studies, in the first study describing increases in the HIV viral load as a consequence of syphilis by Buchacz et al., HIV infection parameters were documented only in a small minority of the studied patients for whom changes in HIV viral load during syphilis were not significant [11]. According to other studies, a minority of HIV-infected patients exhibited an increase in viral load during syphilis [16, 17]. High-risk sexual behaviors may be associated with poorer compliance with the ART [22], which could explain worsening in HIV infection parameters in some of the syphilis-infected HIV-positive patients. However, a protective effect of ART on a slight syphilis-induced replication of HIV cannot be excluded considering the fact that mild increases in viral load were more common among patients without ART. Among patients on ART only two presented an increased viral load at diagnosis of syphilis, despite the fact that the ART regimen appeared effective in both of them as they had a viral load below the detection level before diagnosis as well as after antibiotic treatment of syphilis. One of them was treated with emtricitabin, tenofovir and darunavir/ritonavir and the other with emtricitabin, tenofovir and atazanavir/ritonavir. Newer or more effective antiretrovirals might have prevented this transient upon the antibiotic treatment-reversible increase in viral load.

Increasing rates of syphilis have been observed in many European countries since 2000 [23]. In 2010, 18,000 cases of syphilis were reported in Europe. MSM were more commonly infected, and increasing rates of syphilis seem to be associated with a concurrent infection with HIV. This could be partially explained by incorporation of serologic testing for syphilis in routine monitoring of HIV-positive MSM, as done in our outpatient HIV clinic [24]. In the present study most HIV patients with syphilis were MSM, corroborating MSM as the major risk group.

There are several reports on the failure of treatment of primary and secondary syphilis in HIV-positive patients with standard antibiotic regimens, including the development of neurosyphilis [25–28]. Several studies have tried to identify predictive factors for neurosyphilis among HIV-infected patients, which would confirm the indication of a lumbar puncture. In the study by Marra et al., low $CD4^+$ T cell counts ($\leq 350/\mu l$) were significantly more common among HIV-positive patients with

neurosyphilis [29]. Ghanem et al. additionally evaluated rapid plasma regain (RPR) titers in HIV-positive and syphilis-infected patients without neurologic manifestations. According to their findings, lumbar puncture in patients with $CD4^+$ T cell counts $\leq$ 350/μl and/or RPR titers $\geq$ 1:32 detected all patients with asymptomatic neurosyphilis [30]. According to the study by Libois et al., syphilis serology and particularly high RPR values ($\geq$ 1:32) had a sensitivity of 100% for the diagnosis of neurosyphilis with a negative predictive value of 100% [31], so that a lumbar puncture would be dispensable in case of absence of neurologic manifestations and low RPR titers. However, other studies yielded no stark or significant association between the $CD4^+$ T cell count or syphilis serology titers and neurosyphilis [31, 32]. In a recent study, low $CD4^+$ T cell counts ($\leq$ 350/μl) and high RPR titers ($\geq$ 1:32) reached a positive predictive value for neurosyphilis of 66.7% and 71.4%, respectively, with a combined sensitivity of 78% and a combined positive predictive value of approximately 67% [32]. This means that in > 20% of HIV-positive patients with neurosyphilis, diagnosis would have been missed if performing a lumbar puncture had depended on these criteria. Further, incidence of neurosyphilis appears higher among HIV-positive patients with syphilis [26], and approximately 9% of HIV-positive and syphilis-infected patients have an asymptomatic neurosyphilis [27, 32–34]. Considering all the above-discussed points, the relatively low sensitivity and specificity of cerebrospinal fluid examinations for the diagnosis of neurosyphilis [35, 36] and the devastating consequences of neurosyphilis [37], we routinely offer all HIV-positive patients with syphilis an antibiotic regimen for neurosyphilis. We acknowledge, however, that such an antibiotic regimen deviates from the current guidelines for the therapy of syphilis [15, 38] and may lead to overtreatment in some patients.

We suggest that further optimization of diagnostic criteria for neurosyphilis in HIV-positive patients is needed. Risk of neurosyphilis among HIV-positive patients and the predictive value of syphilis serology, immunologic parameters of HIV infection as well as likely signs and symptoms of neurosyphilis have to be evaluated though multicenter studies to better define the indication of lumbar puncture. Further, the sensitivity and specificity of celebrospinal fluid markers for neurosyphilis have to be further improved; considering its likely devastating consequences, neurosyphilis is a diagnosis not to be missed.

We acknowledge that the present study has certain limitations, including being a single-center study with limited numbers of patients and its retrospective design. However, to our knowledge, this is the first study evaluating total lymphocyte counts, counts of lymphocyte subsets and relative $CD4^+$ T counts during syphilis in HIV-positive patients.

CONCLUSION

In conclusion, our findings suggest that syphilis is unlikely to affect the course of a preexisting HIV infection as a reduction in $CD4^+$ T cell count appears in the context of a non-subset-specific decrease in lymphocyte count and increased viral load values are observed only in a minority of patients. For daily clinical practice our findings suggest that an otherwise unexplained reduction in total lymphocyte count is an early laboratory finding of syphilis and should be a reason for prompt serologic screening for syphilis, especially in case of MSM HIV-infected patients.

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Compliance with Ethics Guidelines. The study was performed in compliance with national policies, the policies of the ethical committee of Hannover Medical University and the 1964 Helsinki Declaration and its later amendments.

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