Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections

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Background: Syphilitic ulcers are known to facilitate the transmission of HIV infection, but the effect of syphilis infection on HIV viral loads and CD4 cell counts is poorly understood.

Methods: We abstracted medical records for HIV-infected male syphilis patients seen at three clinics in San Francisco and Los Angeles from January 2001 to April 2003. We compared plasma HIV-RNA levels and CD4 cell counts during syphilis infection with those before syphilis infection and after syphilis treatment, using the Wilcoxon signed rank test.

Results: Fifty-two HIV-infected men with primary or secondary syphilis had HIV viral load and CD4 cell count data available for analysis; 30 (58%) were receiving antiretroviral therapy. Viral loads were higher during syphilis compared with pre-syphilis levels by a mean of 0.22 RNA $\log_{10}$ copies/ml ($P = 0.02$) and were lower by a mean of -0.10 RNA $\log_{10}$ copies/ml ($P = 0.52$) after syphilis treatment. CD4 cell counts were lower during syphilis infection than before by a mean of -62 cells/mm^3 ($P = 0.04$), and were higher by a mean of 33 cells/mm^3 ($P = 0.23$) after syphilis treatment. Increases in the HIV viral load and reductions in the CD4 cell count were most substantial in men with secondary syphilis and those not receiving antiretroviral therapy.

Conclusion: Syphilis infection was associated with significant increases in the HIV viral load and significant decreases in the CD4 cell count. The findings underscore the importance of preventing and promptly treating syphilis in HIV-infected individuals.

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Introduction

Recent outbreaks of syphilis among men who have sex with men in major US cities [1,2], and reported increases in sexual risk behavior [3,4], have generated concerns about the potential increases in HIV incidence associated with these syphilis epidemics [2]. Epidemiological studies have provided substantial evidence that syphilis infection, one of the causes of genital ulcer disease, facilitates HIV transmission [5–7]. Syphilitic ulcers disrupt epithelium and mucosa, thus aiding the passage of HIV. In addition, syphilis infection, particularly the generalized stage of secondary syphilis, may increase the immune activation of host cells, affect the secretion of cytokines including TNF-α, and upregulate transcription factors such as nuclear factor kappa beta to alter cell cycles, and thus enhance HIV replication [8–11]. Genital ulcer disease may increase HIV viral loads and depress CD4 cell counts [12], but the specific relationship between syphilis and the plasma HIV viral load has not been well described. Other sexually transmitted diseases (STD) [13–15] and infections [9,16] have been linked to increased plasma HIV viral loads and reduced CD4 cell counts; their treatment may reduce the viral load in some [11–14] but not all patients [10,15]. As part of a rapid public health investigation in response to syphilis outbreaks in San Francisco and Los Angeles, we examined changes in the plasma HIV viral load and CD4 cell count associated with incident syphilis infection and its treatment in HIV-infected men diagnosed with syphilis.

Methods

We conducted a retrospective case-series study. San Francisco and Los Angeles county syphilis surveillance databases were first reviewed to identify all HIV-infected men who were diagnosed with primary or secondary syphilis from January 2001 to April 2003. Syphilis surveillance databases include information on the healthcare provider reporting each case. Three clinics that serve HIV-infected gay men and diagnose a large number of syphilis cases were selected as study sites: the Positive Health Program at the San Francisco General Hospital (PHP), the San Francisco City STD Clinic (SFCC), and the AIDS Healthcare Foundation (AHF) in Los Angeles. We identified 89 HIV-infected men with primary and secondary syphilis who were receiving HIV care at the three sites: 43 at PHP and SFCC and 46 at AHF. Demographic and HIV and syphilis-related clinical and laboratory information was collected from medical records and surveillance databases. To be included in the study, HIV-infected men had to have had their plasma HIV viral load measured around the time of syphilis diagnosis, and at least once more before or after syphilis diagnosis, at pre-specified timepoints (as defined below), and had to have been continuously on the same highly active antiretroviral therapy (HAART) regimen or not receiving antiretroviral therapy between the viral load measurements. Of 89 HIV-infected men with syphilis diagnosed at the three study sites, 52 met the inclusion criteria. The 37 men who were excluded were similar to those who were included in terms of race/ethnicity and age distribution.

Plasma HIV viral load measurements below the limit of detection were all less than 75 copies/ml for assays performed at PHP and SFCC and less than 50 copies/ml for assays performed at the AHF, and thus were assigned those absolute values for analysis. In addition, viral loads that were recorded at AHF as greater than 75 000, greater than 100 000 or greater than 500 000 copies/ml were assigned those absolute values (i.e. 75 000, 100 000 or 500 000 copies/ml) for analysis, hereafter referred to as the 'truncated' value. HIV viral loads were analysed after $\log_{10}$ transformation. We compared viral loads and CD4 cell counts during syphilis (during) with those before syphilis diagnosis (before) and after syphilis diagnosis and treatment (after). Consistent with the incubation periods for syphilis, the time periods for analyses were defined as follows. For primary syphilis 'before' was 3–6 months before syphilis diagnosis, 'during' was around the time of syphilis diagnosis (−6 to +2 weeks), and 'after' was 3–9 months after syphilis diagnosis and treatment. For secondary syphilis 'before' was 6–9 months before syphilis diagnosis, 'during' was around the time of syphilis diagnosis (−12 to +2 weeks), and 'after' was 3–9 months after syphilis diagnosis and treatment. We calculated the changes in $\log_{10}$ HIV RNA and CD4 cell counts for the 'before-to-during', 'during-to-after', and 'before-to-after' periods for each individual who had paired data. If multiple viral loads or CD4 cell counts were available for 'before', 'during' or 'after', the measurement nearest to the time of syphilis diagnosis was considered. Intra-individual paired comparisons of laboratory markers were performed using the non-parametric Wilcoxon signed rank test.

Results

The 52 HIV-infected men included in the study had a median age of 36 years (range 20–56); 26 (50%) were white, 19 (37%) were Hispanic, 3 (6%) were black, and the remaining four (8%) were of other race/ethnicity. Of the participants, 35 (67%) had secondary syphilis, 30 (58%) were receiving HAART and 28 (54%) had CD4 cell counts of less than 350 cells/mm^3 at the time of syphilis diagnosis. Of 52 patients, 45 (86%) received one or three doses of benzathine penicillin G 2.4

million units for treatment of syphilis. All except two responded to antibiotic treatment, having at least a fourfold decrease in non-treponemal serological titers at 6 months.

Of 52 patients, 45 (87%) had their 'during' viral load within 3 weeks of syphilis diagnosis. The mean (median) timespan between 'before' and 'during' viral load measurements was 5.7 (6.2) months overall, 4.2 (4.1) months for men with primary syphilis, and 6.7 (6.7) months for men with secondary syphilis.

Overall, the 36 men who had 'before-to-during' viral load data had a significant increase in $\log_{10}$ HIV-RNA copies/ml (mean 0.21) during syphilis infection (Table 1). Viral load increases occurred predominantly in 22 men who had secondary syphilis (mean 0.33) and in 15 men who were not receiving antiretroviral therapy (mean 0.25) (Table 1, Fig. 1). Among the 10 men who had secondary syphilis and who were not on HAART, the viral load was substantially higher during syphilis infection by a mean of 0.34 $\log_{10}$ HIV-RNA copies/ml ($P = 0.05$).

In addition, in analyses stratified by the initial viral load, of the 26 men who had detectable viral loads before syphilis infection, 13 (50%) had a higher viral load during syphilis infection than before infection, with 12 having an increase of at least 0.5 $\log_{10}$ RNA copies/ml. By contrast, of the 10 men who were on HAART and had undetectable HIV viral loads before syphilis infection, only two (20%) had detectable viral loads at the time of syphilis diagnosis.

However, among the 35 men who had 'during-to-after' data, viral loads did not significantly decrease after syphilis treatment overall (mean change −0.10) or in any of the subgroups (Table 1).

In an alternative set of analyses, we examined viral loads in 19 men who had 'before', 'during', and 'after' viral load data, of whom 12 (63%) had secondary syphilis, 13 (68%) had detectable viral loads before syphilis and 15 (79%) were on HAART. Among these 19 men, the mean changes in $\log_{10}$ RNA copies/ml were 0.10 for 'before-to-during', −0.03 for 'during-to-after', and 0.07 for 'before-to-after' comparisons (all $P > 0.2$).

Table 1. Changes in HIV viral load and CD4 cell count associated with syphilis infection and treatment in HIV-infected men.

	'Before-to-during' syphilis infection[a]					'During-to-after' syphilis infection[b]				
Category	No.	Direction of change +/0/−[c]	Mean	Median	*P*	No.	Direction of change +/0/−	Mean	Median	*P*
Change in HIV-RNA levels[d] ($\log_{10}$ copies/ml)										
Overall	36	15/10/11	0.21	0.00	0.02	35	13/7/15	−0.10	0.00	0.52
Stage of syphilis										
Primary	14	4/4/6	0.02	0.00	1.00	10	3/1/6	−0.05	−0.10	0.82
Secondary	22	11/6/5	0.33	0.25	0.01	25	10/6/9	−0.10	0.00	0.65
Antiretroviral use										
On HAART	21	7/8/6	0.19	0.00	0.19	24	10/6/8	−0.05	0.00	0.97
Not on HAART[e]	15	8/2/5	0.25	0.51	0.09	11	3/1/7	−0.18	−0.06	0.23
Viral load level										
Detectable	26	13/2/11	0.20	0.16	0.07	28	12/1/15	−0.11	−0.06	0.48
Undetectable	10	2/8/0	0.25	0.00	0.50	7	1/6/0	−0.08	0.00	1.00
CD4 cell count										
⩾ 350 cells/mm^3	14	6/7/1	0.24	0.00	0.16	19	9/3/7	−0.09	0.00	0.98
< 350 cells/mm^3	21	8/3/10	0.16	0.00	0.32	16	4/4/8	−0.08	−0.03	0.46
Change in CD4 cell count (cells/mm^3)										
Overall	31	12/0/19	−62	−16	0.04	31	20/0/11	33	30	0.23
Stage of syphilis										
Primary	12	4/0/8	−36	−12	0.21	11	7/0/4	24	34	0.62
Secondary	19	8/0/11	−78	−144	0.11	20	13/0/7	38	30	0.12
Antiretroviral use										
On HAART	19	9/0/10	−32	−16	0.31	22	15/0/7	54	32	0.05
Not on HAART	12	3/0/9	−110	−45	0.03	9	5/0/2	−18	14	1.00
Viral load level										
Detectable	21	8/0/13	−79	−15	0.06	24	15/0/9	8	32	0.29
Undetectable	10	4/0/6	−27	−119	0.49	7	5/0/2	119	30	0.30
CD4 cell count										
⩾ 350 cells/mm^3	13	4/0/9	−64	−88	0.21	14	9/0/5	16	28	0.76
< 350 cells/mm^3	18	8/0/10	−60	−16	0.14	17	11/0/6	47	34	0.05

HAART, Highly active antiretroviral therapy.[a]The median timespan for 'before-to-during' changes in 36 men was 6.2 months.[b]The median timespan for 'during-to-after' changes in 35 men was 4.2 months.[c]Indicates how many men had an increase, no change or decrease in measurements.[d]Mean and median values are subject to some viral load values being below the limit of detection and truncated, as described in the text. *P* values obtained by Wilcoxon signed rank test.[e]Indicates men who were not receiving antiretroviral therapy.

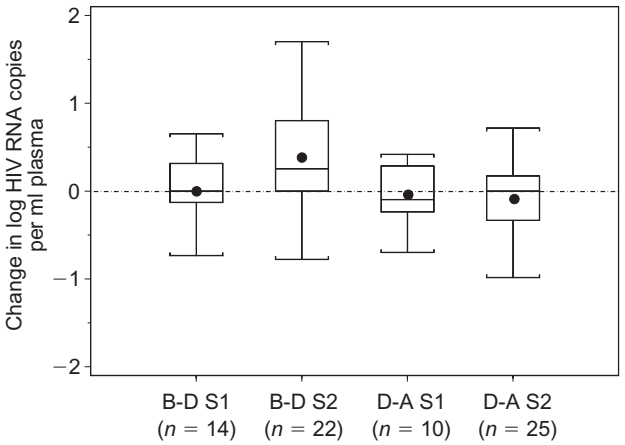

Fig. 1. Changes in HIV viral load associated with syphilis infection and syphilis treatment, according to the stage of syphilis. B–D, 'Before-to-during'; D–A, 'during-to-after'; S1, primary syphilis; S2, secondary syphilis. Boxplots show medians and upper and lower quartiles, whiskers encompass the extent of the data. Means are represented by filled circles.

Among the 31 men who had 'before-to-during' CD4 cell count data, the CD4 cell count decreased significantly during syphilis infection (mean change −62 cells/mm^3). The decreases in CD4 cell count were predominately in men with secondary syphilis, and in men who were not receiving antiretroviral therapy (Table 1). Overall, CD4 cell counts increased but not significantly after syphilis treatment (mean +33 cells/mm^3), but the increases were significant in men who had lower CD4 cell counts and those who were receiving HAART (Table 1). Furthermore, for a subset of 15 men who had CD4 cell count data for 'before', 'during', and 'after', the mean difference 'before-to-after' was +6.5 cells/mm^3 ($P = 1.00$).

Furthermore, using information on other STDs abstracted from medical records in Los Angeles and the San Francisco surveillance data, we identified that 19 out of 52 men had other STDs in addition to syphilis during the time period of analysis. The 'before-to-during' changes in HIV-RNA $\log_{10}$ copies/ml for 22 men who had no other recorded STDs were similar to those for all the men in our study (mean 0.22, $P = 0.12$).

Discussion

Syphilis infection was associated with a significant increase in the plasma HIV viral load and a significant decrease in CD4 cell counts in HIV-infected men. Increases in the HIV viral load occurred predominately in men who had secondary syphilis, which is a more generalized form of disease that might lead to greater immune activation than primary syphilis [8–10]. In agreement with some other studies of HIV-infected patients with co-infections [8,10,15], we found no significant reduction in viral load by 3–6 months after syphilis treatment, which may be related to persistent immune activation, but cannot be explained by syphilis treatment failures in this patient population.

This exploratory retrospective case-series study utilized existing medical records and laboratory data. No systematic data for concurrent infections and immunizations (which may affect HIV viral load and CD4 cell counts) and only limited data on other STDs were available. Plasma HIV viral loads were measured by a variety of assays, and viral load and CD4 cell count measurements were sometimes missing at timepoints of interest. Only 19 out of 52 men in our study population had data for 'before', 'during' and 'after' timepoints, therefore we cannot rule out the possibility of selection bias affecting our findings. In addition, because we studied men who were enrolled in HIV care programs, the results may not be generalizable to all HIV and syphilis-co-infected men. We may have failed to detect some significant changes in the HIV viral load and CD4 cell count in subgroup analyses because of the small sample size and low statistical power, whereas other significant changes might have arisen by chance alone. Finally, our exploratory study did not have a comparison group of HIV-positive men not infected with syphilis. Instead, we examined within-person changes in viral loads and CD4 cell counts, with each man serving as his own control. We acknowledge that, as a result of HIV disease progression, the reported 'before-to-during' changes in viral loads and CD4 cell counts associated with syphilis may be somewhat overestimated, whereas the 'during-to-after' changes may be attenuated [17,18]. Larger confirmatory studies of patients diagnosed with syphilis in HIV care with careful viral load monitoring over longer periods of time may be useful to verify these findings, but probably challenging to conduct.

In conclusion, syphilis infection in HIV-infected men was associated with a significant increase in the HIV viral load and a significant decrease in the CD4 cell count. Because of the overlap in risk behaviors that lead to HIV and syphilis infections, and because syphilis may enhance HIV transmission via the syphilitic ulcers and by raising the HIV viral load [7], integrated public health efforts to prevent new syphilis infections, and to identify and treat syphilis cases promptly, are warranted to reduce the spread of both diseases within affected communities.

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