Impact of Syphilis Infection on HIV Viral Load and CD4 Cell Counts in HIV-Infected Patients

Rosario Palacios, MD, PhD, Francisco Jiménez-Oñate, MD,† Manuela Aguilar, MD,‡ Mª José Galindo, MD, PhD,§ Pablo Rivas, MD,‖ Antonio Ocampo, MD,¶ Juan Berenguer, MD, PhD,# Jose Alberto Arranz, MD,** Mª José Ríos, MD,†† Hernando Knobel, MD, PhD,‡‡ Francisco Moreno, MD,§§ Javier Ena, MD, PhD,‖‖ and Jesús Santos, MD, PhD**

Objectives: To assess the effect of early syphilis on HIV viral load (VL) and CD4 cell count in patients with HIV and to analyze factors associated with changes in HIV VL and CD4 cell count.

Design: Multicenter study of a series of patients with HIV who were diagnosed with early syphilis infection during 2004 through 2005. Patients who started or changed their highly active antiretroviral therapy (HAART) regimen during the analysis period were excluded.

Results: One hundred eighteen patients were analyzed: 95.8% were men, mean patient age was 38.2 years, 83.9% were homosexual men, 50.8% were on antiretroviral therapy at the time syphilis was diagnosed, and HIV and syphilis diagnoses were coincident in 38 (32.2%) cases. CD4 cell counts were lower during syphilis than before (590 vs. 496 cells/μL; $P = 0.0001$) and after syphilis treatment (509 vs. 597 cells/μL; $P = 0.0001$). The HIV VL increased in 27.6% of patients during syphilis. The only factor associated with an HIV VL increase was not being on HAART, and the only factor associated with a CD4 count decrease >100 cells/μL during syphilis was the prior CD4 cell count.

Conclusions: Syphilis infection was associated with a decrease in the CD4 cell count and an increase in the HIV VL in almost one third of the patients. In this series, more than two thirds of the syphilis cases were diagnosed in patients who were previously known to be infected with HIV.

Key Words: CD4 cell count, HIV infection, HIV viral load, homosexual, sexually transmitted diseases, syphilis

(*J Acquir Immune Defic Syndr* 2007;44:356–359)

Because syphilis and HIV infections are similarly transmitted, coinfection is not unusual.[1] Increases in sexual risk behavior and outbreaks of syphilis among men who have sex with men have recently been reported,[2–10] which has generated concerns about the potential increases in HIV incidence associated with these syphilis epidemics.[11] In addition, syphilis infection may increase the immune activation of host cells and the secretion of cytokines, and thus enhance HIV replication.[12–14] Moreover, genital ulcer disease may increase plasma HIV viral load (VL) and depress CD4 cell counts.[14] Although increases in HIV VLs and decreases in CD4 cell counts have recently been reported in HIV patients with a new syphilis infection,[15,16] the interaction between syphilis and these variables is not well defined. Accordingly, we aimed to assess the effect of early syphilis on HIV VLs and CD4 cell counts in HIV-infected patients and to analyze factors associated with changes in HIV VLs and CD4 cell counts.

PATIENTS AND METHODS

We conducted a multicenter case series study of patients coinfected with HIV and syphilis. Databases from 12 Spanish hospitals were first reviewed to identify all HIV-infected patients who were diagnosed with early syphilis infection (<2 years) from January 2004 to December 2005. Syphilis diagnosis was based on positive serologic test results, including a nontreponemal antibody test and a specific treponemal antibody test. In addition, to be included in the study, all patients had to have had their HIV VL measured around the time of the syphilis diagnosis and at least once more before and/or after the diagnosis of syphilis at the time points defined in this article. In all departments, the Ultrasensitive Method (Roche Molecular Systems, Branchburg, NJ) was used to determine HIV RNA levels (detection limit of 50 copies/mL). Patients who started or changed their highly active antiretroviral therapy (HAART) regimen during the study period were excluded. We compared plasma HIV VL measurements and CD4 cell counts "before" (3–9 months before the diagnosis of syphilis), "during" (between −12 and 2 weeks before the date when syphilis was diagnosed), and "after" (3–9 months after the diagnosis and treatment of syphilis) the diagnosis of syphilis. The changes in $\log_{10}$ HIV VL and CD4 cell count for the "before-to-during" and "during-to-after" periods for each patient who had paired data were calculated. The increase in HIV VL during syphilis was defined as an

Received for publication July 17, 2006; accepted November 10, 2006.
From the *Hospital Virgen de la Victoria, Málaga, Spain; †Hospital Carlos Haya, Málaga, Spain; ‡Hospital Virgen del Rocío, Sevilla, Spain; §Hospital General, Valencia, Spain; ‖Hospital Carlos III, Madrid, Spain; ¶Hospital Xeral, Vigo, Spain; #Hospital Gregorio Marañón, Madrid, Spain; **Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain; ††Hospital Virgen Macarena, Sevilla, Spain; ‡‡Hospital del Mar, Barcelona, Spain; §§Hospital Costa del Sol, Marbella, Spain; and ‖‖Hospital de Villajoyosa, Alicante, Spain.
Reprints: Jesús Santos, MD, PhD, Infectious Diseases Unit, Campus Teatinus, s/n 29010 Málaga, Spain (e-mail: med000854@saludalia.com).

increase ≥ 0.5 $\log_{10}$ with respect to the "before" syphilis value, or a detectable HIV VL for those previously suppressed patients, and the decrease in CD4 cell count was defined as a decrease ≥ 100 cells/μL with respect to the "before" syphilis value. To assess factors associated with an increase in HIV VL and factors associated with a decrease in CD4 cell count during syphilis, 2 logistic regression models were applied in which all factors meeting the criterion of $P < 0.2$ on univariate analysis were included. The statistical analysis was performed with SPSS, version 12.0 for Windows (SPSS, Chicago, IL).

RESULTS

We identified 151 patients with HIV who also had early syphilis, and 118 of them met the inclusion criteria for study entry. Twenty patients were excluded because they started or changed HAART during the study period, and 13 other patients were excluded because of a lack of inmmunovirologic data around the time of the diagnosis of syphilis. The characteristics of these patients are shown in Table 1. All patients received treatment for syphilis with standard doses of benzathine penicillin. Other coincident sexually transmitted diseases or opportunistic infections during syphilis infection were not diagnosed in the study patients, and there was no vaccine administration during the study period.

With respect to HIV VL, it increased in 21 of the 76 patients for whom "before" and "during" measurements were available. Ten (33.3%) of the 32 patients with a prior detectable HIV VL demonstrated a mean HIV VL increase of 1.03 $\log_{10}$ (interquartile range [IQR]: 0.64–1.32 $\log_{10}$) during syphilis, and 11 (25.0%) of those patients with a suppressed HIV VL before syphilis (n = 44) had a detectable HIV VL during the syphilis infection (mean HIV VL increase of 1.46 $\log_{10}$, IQR: 0.32–3.21 $\log_{10}$). In addition, in 9 (42.8%) of 21 patients, the increase in HIV VL persisted after syphilis treatment. Patients on HAART were at lower risk for demonstrating an increase in HIV VL during syphilis (Table 2). Overall, the 76 patients who had "before-to-during" data demonstrated a significant decrease in their CD4 cell count during syphilis infection and the 94 patients who had "during-to-after" data demonstrated a significant increase in their CD4 cell count after the syphilis episode (Fig. 1). The only factor associated with a CD4 count decrease >100 cells/μL during syphilis was the prior CD4 cell count (see Table 2). There were no differences in the immunologic and virologic evolution according to the stage of syphilis.

TABLE 1. Clinical and Biologic Characteristics of the 118 Patients

Variable	n (%)
Male gender	113 (95.8)
Age (y)	38.2 (33.1–42.2)
HIV transmission category	
Homosexual contacts (men with men)	99 (83.9)
Heterosexual contacts	10 (8.5)
IDU	7 (5.9)
Others	2 (1.6)
Estimated duration of HIV infection (mo)	59.1 (0.8–109.6)
AIDS cases	21 (17.8)
Patients on HAART	60 (50.8)
CD4 counts (cells/μL)	586 (351–736)
HIV RNA ($\log_{10}$ copies/mL)	4.71 (2.76–4.34)
HIV RNA <50 copies/mL	44 (37.3)
HIV-syphilis coincident diagnosis	38 (32.2)
First syphilis episode	100 (84.7)
Syphilis symptomatology	
Asymptomatic	35 (29.7)
Symptomatic	83 (70.3)
Secondary syphilis	57
Chancre	18
Other symptoms	8

Quantitative variables are expressed as mean (IQR).
Qualitative variables are expressed in absolute values and percentages.
IDU indicates intravenous drug use.

DISCUSSION

In this series, syphilis infection was associated with a significant increase in HIV VL in 28.0% of patients and a decrease in CD4 cell count, which was greater among those patients with a better immunologic status.

The conjunction of syphilis and HIV infections may have important epidemiologic and clinical consequences. A worrisome finding in our series, which is in line with other studies,[17] is that more than two thirds of the syphilis cases were diagnosed in previously known HIV-infected patients, many of whom were on HAART, which highlights the risky behavior of our patients and the weak preventive strategies.

Increases in plasma HIV VL during sexually transmitted diseases and other infections have long been reported.[12–14,18,19] In agreement with 2 recent studies,[15,16] we confirm that this is also the case in patients who are coinfected with HIV and syphilis. It has been suggested that increases in HIV VL occur mainly in patients with secondary syphilis.[12,13,15] In our study, there was no difference in the virologic change, depending on the stage of syphilis. Although a considerable proportion of previously suppressed patients who were on HAART had a detectable VL during syphilis, the only factor associated with an increase in HIV VL was not being on HAART. In line with data reported in several studies of HIV-infected patients with coinfections,[12,15] we found no reduction in VL after syphilis treatment. These findings may be related to persistent immune activation.[12,13]

Concerning CD4 cell changes during follow-up, syphilis infection was clearly associated with a decrease in CD4 cell count, as has also been reported by others.[15,16] The fact that more than one half of our patients were on HAART may have limited the degree of the impact of syphilis on CD4 cell levels. Nevertheless, we observed that CD4 cell counts decreased in HIV patients on HAART and in those not on HAART. Kofoed et al[16] suggested that the effects of syphilis may be much more limited in patients who are more immunologically compromised. In our series, most patients were quite well maintained immunologically and the CD4 cell count decreased in the series overall. In agreement with Kofoed et al,[16] however, we did observe a greater CD4 cell count decrease among patients

TABLE 2. Factors Associated With an Increase in HIV VL (>0.5 Log_{10}) and a CD4 Count Decrease (≥100 Cells/μL) During Syphilis

	Univariate			Multivariate		
	Increase in HIV VL (n = 21)	**No Increase in HIV VL (n = 55)**	***P***	**β Coefficient**	**(95% CI)**	***P***
Age	38.2 (30.1–41.2)	39.6 (35.0–44.5)	0.51			
Male gender	19 (90.4)	53 (96.3)	0.30			
HMX category risk	17 (80.9)	47 (85.4)	0.46			
Estimated duration of HIV (mo)	75.8 (28.2–129.6)	87.6 (33.0–143.2)	0.41			
AIDS cases	5 (23.8)	13 (23.6)	1.0			
Patients on HAART	11 (52.3)	45 (81.8)	0.01	0.30	0.09–0.95	0.04
Time on HAART (mo)	23.9 (9.9–37.2)	24.1 (10.7–29.7)	0.96			
First syphilis episode	14 (66.6)	45 (81.8)	0.34			
Systemic syphilis symptomatology*	11 (52.3)	30 (54.5)	1.00			
RPR >1/64†	5 (23.8)	15 (27.2)	0.77			
Baseline CD4 counts (cells/μL)	504 (350–696)	608 (351–761)	0.19			
Baseline CD4 >500 cells/μL	10 (47.6)	32 (58.1)	0.79			
Baseline HIV VL (log_{10})	3.4 (2.3–4.3)	3.7 (2.7–4.6)	0.25			
HIV RNA <50 copies/mL	8 (38.0)	35 (63.6)	0.11			
	Decrease in CD4 (n = 33)	**No Decrease in CD4 (n = 43)**	***P***	**β Coefficient**	**(95% CI)**	***P***
Age	37.6 (34.1–42.7)	40.7 (35.5–44.5)	0.11			
Male gender	31 (93.9)	41 (95.3)	1.0			
HMX HIV transmission	27 (81.8)	37 (86.0)	0.92			
Estimated duration of HIV (mo)	82.1 (30.1−−148.2)	91.4 (36.7−−136.4)	0.52			
AIDS cases	5 (15.1)	13 (30.2)	0.17			
Patients on HAART	22 (66.6)	35 (81.3)	0.18			
Time on HAART (mo)	22.8 (13.7–30.4)	24.7 (8.8–30.4)	0.69			
First syphilis episode	28 (84.8)	31 (72.0)	0.15			
Systemic syphilis symptomatology*	19 (57.5)	21 (48.8)	0.49			
RPR >1/64†	6 (21.4)	14 (32.5)	0.28			
Baseline CD4 counts (cells/μL)	761 (606–881)	460 (204–684)	0.0001			
Baseline CD4 >500 cells/μL	27 (81.8)	18 (41.8)	0.0001	6.61	2.5–19.4	0.0001
Baseline HIV VL (log_{10})	3.8 (3.2–4.4)	3.4 (2.6–4.4)	0.40			
Baseline HIV RNA <50 copies/mL	19 (57.5)	25 (58.1)	1.0			

*Systemic syphilis includes secondary and other clinical forms, except for chancre.
†Data were missing in 8 cases. Data shown are expressed as n (%) or mean (IQR).
95% CI indicates 95% confidence interval.

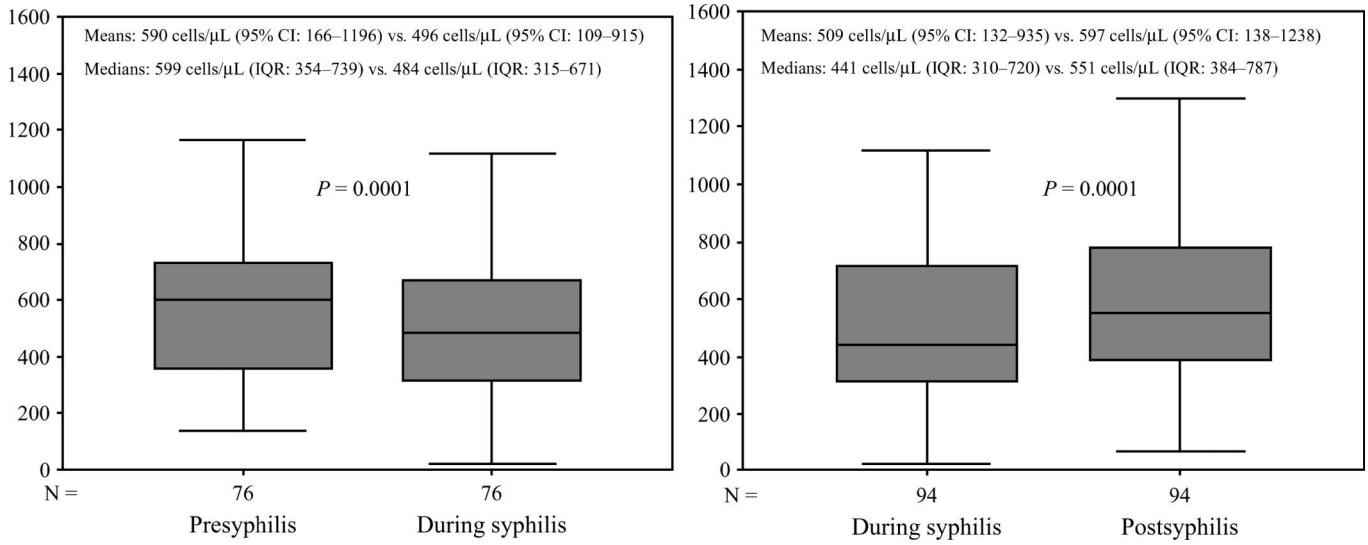

FIGURE 1. Evolution of CD4 cell counts during the study period.

with a higher baseline CD4 cell count, and in addition, the only factor associated with a CD4 decrease >100 cells/μL was the CD4 cell count before syphilis. As expected, patients on HAART who were followed for the whole study period demonstrated an increase in their CD4 cell count after syphilis treatment.

We acknowledge that our study has certain limitations, such as its retrospective design and the lack of a control group of HIV patients not infected with syphilis. The VL and CD4 cell measurements also were occasionally missing at some time points of the study. Conversely, we need to highlight that the study included a large sample of patients. As far as we are aware, ours would be the third and largest study to date to evaluate the impact of syphilis infection on HIV VL and CD4 cell counts. In addition, ours is the only study that analyzes factors associated with changes in HIV VL and CD4 cell count during syphilis.

In summary, syphilis infection in HIV-infected patients was associated with a significant decrease in CD4 cell count and an increase in plasma HIV VL. Our data also confirm the information provided by recent epidemiologic studies of syphilis outbreaks among men who have sex with men. Integrated public health efforts to prevent new syphilis infections and to identify and treat affected patients as soon as possible are therefore warranted to reduce the spread of both diseases within this population.

REFERENCES

1. Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. *Lancet Infect Dis*. 2004;4:456–466.
2. Centers for Disease Control and Prevention. Increases in unsafe sex and rectal gonorrhea among men who have sex with men. San Francisco, California, 1994–1997. *MMWR Morb Mortal Wkly Rep*. 1999;48:45–48.
3. Dodds JP, Nardone A, Mercey DE, et al. Increase in high risk sexual behaviour among homosexual men, London 1996–1998: cross-sectional, questionnaire study. *BMJ*. 2000;320:1510–1511.
4. Pérez K, Rodés A, Casabona J. Monitoring HIV prevalence and behaviour of men who have sex with men in Barcelona, Spain. *Eurosurveillance*. 2001;7:23–28.
5. Centers for Disease Control and Prevention. Transmission of primary and secondary syphilis by oral sex—Chicago, Illinois, 1998–2002. *MMWR Morb Mortal Wkly Rep*. 2004;53:966–968.
6. Vall Mayans M, Sanz Colomo B, Loureiro Varela E, et al. Infecciones de transmisión sexual en Barcelona más allá del 2000. *Med Clin (Barc)*. 2004;122:18–20.
7. Potthoff A, Brockmeyer NH. Syphilis and HIV infection. Characteristic features of diagnosis, clinical assessment, and treatment. *Hautartz*. 2005; 56:133–140.
8. Lavigne JP, Rouanet I, Gleize E, et al. Resurgence of syphilis: a prospective study at a University Hospital, Nimes. *Rev Med Interne*. 2004;25:715–719.
9. Kingston MA, Higgins SP. Audit of the management of early syphilis at North Manchester General Hospital. *Int J STD AIDS*. 2004;15:352–354.
10. Dupin N, Couturier E. Syphilis, new epidemiologic features. *Rev Prat*. 2004;54:371–375.
11. Cohen MS. When people with HIV get syphilis: triple jeopardy. *Sex Transm Dis*. 2006;33:149–150.
12. Bentwich Z, Maartens G, Torten D, et al. Concurrent infections and HIV pathogenesis. *AIDS*. 2000;14:2071–2081.
13. Sulkowski MS, Chaisson RE, Karp CL, et al. The effect of acute infections illnesses on plasma human immunodeficiency virus (HIV) type 1 load and the expression of serologic markers of immune activation among HIV-infected adults. *J Infect Dis*. 1998;178:1642–1648.
14. Dyer JR, Eron JJ, Hoffman IF, et al. Association of CD4 cell depletion and elevated blood and seminal plasma human immunodeficiency virus type 1 (HIV-1) RNA concentrations with genital ulcer disease in HIV-1 infected men in Malawi. *J Infect Dis*. 1998;177:224–227.
15. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. 2004;18:2075–2079.
16. Kofoed K, Gerstoft J, Mathiesen LR, et al. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV viral load, and treatment response. *Sex Transm Dis*. 2006;33: 143–148.
17. Vall-Mayans M, Casals M, Vives A, et al. Reemergence of infectious syphilis among homosexual men and HIV coinfection in Barcelona, 2002–2003. *Med Clin (Barc)*. 2006;126:94–96.
18. Donovan RM, Busch CE, Markowitz NP, et al. Changes in virus load markers during AIDS-associated opportunistic diseases in human immunodeficiency virus-infected persons. *J Infect Dis*. 1996;174:401–403.
19. Busch CE, Donocan RM, Markowitz NP, et al. A study of HIV RNA viral load in AIDS patients with bacterial pneumonia. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;13:23–26.