Early Syphilis Often Missed in HIV-Positive Men

BY NANCY WALSH
New York Bureau

BOSTON — The diagnosis of syphilis is often delayed in HIV-positive patients, as it is characterized by a wide range of symptoms that may not be recognized as infection with *Treponema pallidum,* according to Dr. Lawrence A. Siegel of the division of international medicine and infectious diseases, Cornell University, New York.

After declining to an all-time low in 2000, the rate of syphilis in the United States rose from 3 per 100,000 population in 2001 to 5.7 per 100,000 in 2006. Syphilis has increased particularly dramatically in men who have sex with men (MSM), who made up 4% of cases in 2000 but who represented 64% of cases in 2006, Dr. Siegel reported in a poster session at the 15th Conference on Retroviruses and Opportunistic Infections.

Nationwide, approximately 60% of cases of syphilis now are seen in HIV-positive, urban MSM, but in New York City, 97% of syphilis cases are in MSM.

To more fully characterize this coinfected population in New York City, Dr. Siegel and his colleagues undertook a retrospective chart review of all HIV-positive MSM diagnosed with incident syphilis at the Cornell HIV clinic between January 2001 and December 2007.

A total of 118 cases of syphilis were identified. Stage at diagnosis was primary in 8 patients, secondary in 80, early latent in 17, and late latent in 13, Dr. Siegel reported. Three patients had neurosyphilis.

Median age of the patients was 38 years. A total of 33% were white, 30% were black, 34% were Hispanic, and the rest were classified as "other." The HIV RNA level was less than 400 copies/mL in 56%, and median CD4 count was 399 cells/mm^3. Rapid plasma regain (RPR) titer at the time of syphilis diagnosis was 1:8 or lower in 17%, 1:16 to 1:32 in 36%, 1:64 to 1:128 in 37%, and higher than 1:256 in 10%.

Clinical presentations were varied, and the diagnosis was delayed in nearly half of the patients overall. (See box.)

A total of 96% of patients had a fourfold decrease in RPR titer at 1 year, but reinfections were common, at a rate of 10% a year.

A multivariate analysis found that higher baseline RPR titer and diagnosis of latent syphilis were associated with a longer time until the RPR titer became negative, Dr. Siegel reported at the meeting, which was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention.

Different treatment regimens (one or three doses of 2.4 million U benzathine penicillin, or doxycycline 100 mg twice daily for 30 days) weren't tied to a longer time until RPR negativity, the researchers said. Cases of early syphilis in this population are often not identified, so a higher index of suspicion is needed. More frequent serologic testing also is warranted. ■

Delays in Syphilis Diagnosis Vary With Presenting Symptoms in HIV-Positive Patients

Symptom	Patients with delay in diagnosis	Median delay (days from symptom onset)
Mouth ulcers (n = 13)	69%	78
Sore throat (n = 25)	56%	44
Cervical lymphadenopathy (n = 23)	52%	56
Chancre (n = 13)	46%	73
Inguinal lymphadenopathy (n = 13)	46%	36
Subjective fever (n = 18)	39%	42
Generalized rash (n = 70)	23%	25
Rash on palms and soles (n = 44)	9%	7

Note: Based on data for 118 syphilis cases in HIV-positive patients.
Source: Dr. Siegel

ELSEVIER GLOBAL MEDICAL NEWS

Lack of Circumcision, Immunity Linked to HIV Vaccine Failure

BY DIANA MAHONEY
New England Bureau

BOSTON — The increased risk of HIV infection observed in the now-defunct trial of Merck's experimental trivalent HIV vaccine V520 was greatest in uncircumcised men with high preexisting immunity to the vaccine's delivery vector, the adenovirus type 5, according to a post hoc analysis of the trial data.

"Uncircumcised men with high immunity to [adenovirus type 5] were more than four times more likely to develop HIV infection than men given the placebo vaccine," Dr. Susan Buchbinder reported at the 15th Conference on Retroviruses and Opportunistic Infections.

The international clinical trial of V520 was halted in September 2007 because it failed to block or slow the rate of HIV infections in the high-risk study population (primarily gay men and female sex workers who had multiple sex partners in the 6 months prior to study initiation). Additionally, the HIV infection rate was higher in the vaccine arm than in the placebo arm, said Dr. Buchbinder of the San Francisco Department of Public Health.

Overall, 49 of 914 vaccine recipients developed HIV infection, compared with 33 of 922 placebo recipients. Because all but one of the reported infections occurred among the study's male volunteers, post hoc analyses have concentrated on the men in the study, she said.

Although the difference in infection rates between the vaccine and placebo groups across the entire study population was only "marginally statistically significant," in the subgroup of participants with high levels of adenovirus type 5 (Ad5) immunity—defined as antibody levels greater than 200 U—the statistical significance between the two groups was more robust. In univariate and multivariate models, high Ad5 immunity was associated with a threefold increased risk of HIV infection in vaccine recipients, Dr. Buchbinder noted.

Univariate and multivariate analyses also identified the lack of circumcision as a risk factor for infection. "Uncircumcised males [with high Ad5 immunity] who received the vaccine were approximately four times more likely than those who received placebo to become infected with HIV," Dr. Buchbinder reported. Circumcision, on the other hand, appeared to blunt the increased vulnerability to infection associated with Ad5 immunity, in that the HIV infection risk among circumcised men with high titers to Ad5 was not statistically significant, she said. Similarly, the increased infection risk observed in uncircumcised men with low titers was not statistically significant.

Men in the study with high Ad5 immunity tended to come from countries and communities with low rates of circumcision.

An evaluation of viral loads across the study population did not identify an obvious correlation between Ad5 immunity and viral load. "We are awaiting additional data on herpes simplex virus 2, [human leukocyte antigen] typing, and sexual network clustering to explore possible confounding factors for HIV acquisition," Dr. Buchbinder added.

The conference was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention. ■

Two Nucleoside Analogues Shown to Increase Risk of MI

BY DIANA MAHONEY
New England Bureau

BOSTON — Recent use of the nucleoside analogues abacavir and didanosine is associated with a significantly increased risk of myocardial infarction in HIV-infected individuals, whereas treatment with the thymidine analogues appears to convey no such risk, according to findings presented at the 15th Conference on Retroviruses and Opportunistic Infections.

Using data from the DAD (Data Collection of Adverse Effects of Anti-HIV Drugs) study, a prospective study of more than 33,000 patients from 11 existing cohorts in Europe, Australia, and the United States, Dr. Caroline Sabin of the Royal Free Hospital, London, and her colleagues determined previously that antiretroviral treatment as a whole and protease inhibitor use specifically were associated with an increased risk of cardiovascular disease.

In the current study, 517 myocardial infarctions occurred during the approximately 7 years of follow-up. The study, which looked at the effect of five individual nucleoside reverse transcriptase inhibitors (NRTIs), showed that treatment with abacavir (Ziagen) was associated with a 90% increased risk of MI, and didanosine was associated with a 49% increased risk. Neither of the thymidine analogues—zidovudine or stavudine—nor the nucleoside analogue lamivudine was associated with increased MI risk, Dr. Sabin said. She reported no conflicts of interest pertaining to the study drugs.

The findings were unexpected, she noted, in that the current investigation was undertaken to test the hypothesis that thymidine analogues, because of their known association with dyslipidemia and insulin resistance, might also be associated with an increased risk of heart attack in HIV-infected individuals.

To assess the effect of cumulative, recent (defined as current or within the past 6 months), and past (defined as outside the past 6 months) use of the five NRTIs, the investigators generated Poisson regression models, adjusting for various factors.

Neither cumulative nor recent use of the two thymidine analogues or lamivudine was associated with risk of MI, whereas recent use of abacavir and didanosine predicted risk of MI, Dr. Sabin reported. Additionally, the risks of MI associated with recent abacavir and didanosine use were independent of duration of use and remained after adjustment for HIV-RNA levels, CD4 count, dyslipidemia, and other metabolic factors, she said. Past use of both drugs was not associated with increased risk of MI, which suggests that the unknown biological mechanism for increased MI risk may be reversible upon cessation of the drugs, she added.

To determine the absolute risk of MI among nucleoside analogue users, the investigators incorporated the Framingham predicted 10-year coronary heart disease risk into the main regression model, and determined that the rate of MI was increased by 119% in patients with a moderate 10-year risk and by 222% in patients with a high 10-year risk, relative to those with a low 10-year risk, Dr. Sabin reported. As such, the clinical implications of the findings depend on an individual patient's underlying cardiovascular risk, she said.

The conference was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention. ■