

Early Syphilis Often Missed in HIV-Positive Men

BY NANCY WALSH
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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 among 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 coinfecting 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/mm³. 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.)

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

A total of 96% of patients had a fourfold decrease in RPR titer at 1 year, but reinfections were common, being seen at a rate of 10% per 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—were not associated with a longer time until RPR negativity, the researchers found. ■

Azithromycin-Resistant *T. pallidum* Strains on Rise in San Francisco

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

CHICAGO — Azithromycin-resistant strains of *Treponema pallidum* continue to emerge in San Francisco, despite cessation of the drug's use for syphilis treatment and prophylaxis, and for the treatment of nongonococcal urethritis in gay men.

The city's 5% resistance rate jumped to 40% in 2003, just a year after the San Francisco Department of Public Health began using the drug prophylactically in the sex partners of gay men with symptomatic syphilis, Dr. Kenneth Katz said at a conference on STD prevention sponsored by the Centers for Disease Control and Prevention.

During this time, azithromycin also was used to treat both syphilis and nongonococcal urethritis in gay men who were allergic to penicillin. But despite a 2004 decision to stop using the drug for any syphilis treatment, resistance has risen linearly each year, to a high of 77% in 2006, said Dr. Katz, a public health official with the CDC and the San Francisco Department of Public Health.

In 1998, gay men made up only 20% of the syphilis cases in San Francisco. By early 2002, that proportion had risen to 90%, said Dr. Katz. The increase spurred the city's health department to launch an aggressive program aimed at decreasing the spread of the disease. "Part of our response was

to treat the sex partners of symptomatic patients with a single 1-g dose of azithromycin. Symptomatic patients who were allergic to penicillin were treated with a single 2-g dose."

The protocol began in July 2002. Soon after, "we began to notice treatment failures in patients with primary or incubating syphilis who had been treated with azithromycin," he said. Azithromycin kills microbes by binding to the ribosome to inhibit protein synthesis. Some strains of *T. pallidum* had developed a mutation that inhibited this ribosomal binding.

In September 2004, the city's health department ceased using azithromycin for any syphilis treatment. But a case-control study showed that the resistant mutation was associated with any azithromycin use within 30 days prior to the syphilis diagnosis. Therefore, Dr. Katz said, the azithromycin ban was extended; in 2005, its use was discontinued in nongonococcal urethritis in gay men.

Despite these precautions, azithromycin resistance has continued to increase, he said. The department conducted a polymerase chain reaction assay on samples from 39 positive lesions in 2005 and 2006. Almost all cases (36) were in gay men. Of the 17 lesions sampled in 2005, 13 (76%) contained the resistant strain. In 2006, 17 (77%) contained the strain. ■

Single-Dose Drug Matches Penicillin for Syphilis Tx

BY MICHELE G. SULLIVAN
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CHICAGO — A single 2-g dose of azithromycin cures early syphilis as effectively as injected penicillin G benzathine, Dr. Edward W. Hook III said at a conference on STD prevention sponsored by the Centers for Disease Control and Prevention.

However, Dr. Hook cautioned that the federally sponsored randomized controlled trial did not include any HIV-positive patients, so its results can't support the use of azithromycin in this population.

"This is the very group in which macrolide-resistant *Treponema pallidum* mutations have emerged in association with azithromycin treatment," said Dr. Hook of the University of Alabama, Birmingham. "I would certainly not recommend treating these patients with azithromycin for early syphilis."

Neither should the drug be used for syphilis in pregnant women. "In light of the history of macrolide treatment failures among pregnant women, I would caution very, very strongly against treating them with azithromycin for syphilis," Dr. Hook said.

The trial compared the efficacy and safety of 2 g of azithromycin given orally with those of 2.4 million U of penicillin G benzathine in 517 patients with early syphilis. Most of the patients (80%) were in Madagascar; the rest were seen at U.S. clinics.

Patients' mean age was 24 years; 26% had primary syphilis, 46% had secondary syphilis, and 28% had presumed early latent syphilis (a sexual partner in the past 12 months with confirmed syphilis).

Serologic cure rates at 3 months were similar in both groups in the intent-to-treat analysis (74% azithromycin vs. 76% penicillin). At 6 months, the cure rates were still not significantly different (77% azithromycin vs. 78% penicillin). Results at 3 and 6 months in the per-protocol analysis were almost identical, Dr. Hook said.

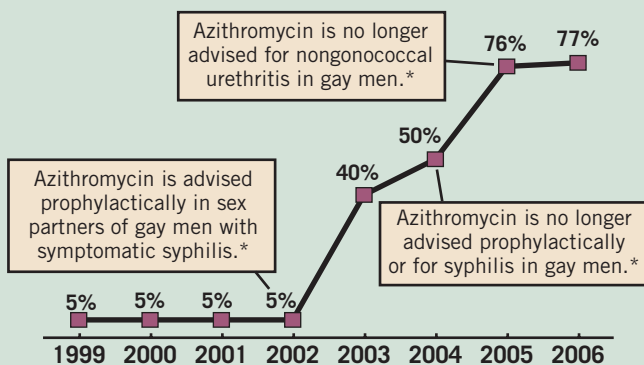
U.S. patients exhibited slightly, but not significantly, higher cure rates than patients in Madagascar.

Serious adverse events were slightly more common in the penicillin group than they were in the azithromycin group (10 vs. 8, respectively). However, none of these was considered related to the study medication. Nonserious adverse events, especially gastrointestinal distress, were significantly more common among the patients taking azithromycin (61% vs. 46% for penicillin).

The most common adverse events were gastrointestinal, with 24% of the azithromycin group and 7% of the penicillin group experiencing some upset. However, only three patients taking azithromycin vomited.

Cutaneous reactions were more common among those taking penicillin (4% vs. 1%), as were administration-related adverse events (10% vs. 5%). ■

Rising Rates of Azithromycin-Resistant *T. pallidum* in San Francisco



*Landmark decisions made by the San Francisco Department of Public Health.
Source: Dr. Katz