Perspective

The Increasing Importance of Sexually Transmitted Diseases in HIV-Infected Persons

Increases in the incidence of sexually transmitted disease (STD) in some locales indicate that safe sex practices are declining and raise concerns about a potential increase in the incidence of HIV infection. Practitioners should renew their vigilance in sexual risk assessment and counseling and be aware of current recommendations for diagnosis and treatment of STDs in HIV-infected patients. This article reviews current recommendations for screening, diagnosis, and management of genital herpes simplex virus infection, chlamydial and gonococcal infections, syphilis, and human papillomavirus–associated neoplasia in HIV-infected patients. The article summarizes a presentation given by Melanie M. Taylor, MD, MPH, at the March 2003 International AIDS Society–USA course in Los Angeles.

There has been an increase in sexual behaviors placing individuals at risk of HIV infection and other sexually transmitted diseases (STDs) in many locales during the recent past, as indicated both by clinicians' findings in risk assessments and by increases in incidence of a number of STDs (Chen et al, *Am J Public Health,* 2002; Ciesielski, *Curr Infect Dis Rep*, 2003; Flaks et al, *Sex Transm Dis,* 2003; Rietmeijer et al, *Sex Transm Dis,* 2003). The increase in risk behaviors among HIV-seropositive men who have sex with men (MSM) may be related to gains in health status and sense of well-being achieved with effective antiretroviral therapy, as well as to general burnout over messages regarding the need for safe sex practices (Dilley et al, *N Engl J Med,* 1997; Flaks et al, *Sex Transm Dis,* 2003). It is important that physicians providing HIV-related care revisit recommendations for evaluating patients for unsafe sex and STDs, and for treating STDs. A summary of the Centers for Disease Control and Prevention's treatment guidelines appears in the Appendix.

STD Evaluation and Prevention Methods

It is crucial that physicians take responsibility for thoroughly discussing sexual risk behaviors with their patients and for encouraging their HIV-infected patients to take responsibility for their HIV disease, which includes informing their sex partners of their infection status. Patients must be informed that presence of STDs is associated with increased risk of HIV transmission. Additional components of STD risk-reduction counseling include performing a thorough STD/HIV sexual risk assessment (including history of anonymous partners, number of sexual partners, discussion of HIV serostatus, and use of drugs associated with heightened sexual activity); providing client-centered prevention counseling; and providing education about appropriate condom use and recognition of STD symptoms. In some locales, including Los Angeles County, MSM report a high frequency of sex with anonymous partners (partners without identifying or contact information) met in commercial sex venues, such as bathhouses and sex clubs, as well as through the Internet, presenting a significant challenge for disease control.

Counseling on prevention methods should include review of appropriate and inappropriate spermicide use, with emphasis on the fact that spermicides alone are not recommended for STD/HIV infection prevention. Nonoxynol-9 vaginal spermicides are not effective in preventing chlamydial, gonococcal, or HIV infections and should not be used as a microbicide or lubricant during vaginal or anal intercourse. In addition, frequent use of spermicides/nonoxynol-9 has been associated with genital lesions. Latex condoms, when used consistently and correctly, are highly effective in preventing transmission of HIV. In addition, correct and consistent use of latex condoms can reduce the risk of other sexually transmitted diseases, including discharge diseases such as chlamydia, gonorrhea, and trichomoniasis as well as genital ulcer diseases, such as herpes simplex virus (HSV), syphilis, and chancroid when the infected area or site of potential exposure is protected. While the effect of condoms in preventing human papillomavirus (HPV) is unknown, condom use has been associated with a lower rate of cervical cancer, an HPV-associated disease.

Patients with newly diagnosed HIV infection should be thoroughly evaluated for STDs, including screening for gonococcal and chlamydial infections, and obtaining syphilis and viral hepatitis serologies. STD screening should be performed at least annually in sexually active persons and every 3 to 6 months in highest-risk MSM (eg, those who acknowledge having multiple anonymous partners or having sex in conjunction with illicit drug use and patients whose sex partners participate in these activities, and persons with previous history of STD or belonging to a patient population with a high prevalence of STDs), including syphilis serology, screening for gonococcal and chlamydial urethral infection by culture or nucleic acid amplification tests, and screening for pharyngeal or rectal gonococcal or chlamydial infections by culture if there is a history of oral-genital or receptive anal intercourse.

Genital HSV Infection

HIV-infected patients with genital HSV infection may have prolonged or severe episodes of reactivation with extensive genital or perianal disease. Episodic or suppressive antiviral therapy often is

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beneficial for treating genital HSV infections. For severe cases, or those with complications requiring hospitalization, treatment with acyclovir 5 to 10 mg/kg intravenously (IV) every 8 hours may be necessary. Recommendations for episodic therapy consist of acyclovir 400 mg 3 times a day, famciclovir 500 mg twice a day, or valacyclovir 1 g twice a day for 5 to 10 days. Daily suppressive therapy can be performed with acyclovir 400 to 800 mg 2 or 3 times a day, famciclovir 500 mg twice a day, or valacyclovir 500 mg twice a day. Antiviral-resistant HSV is found in approximately 5% of immunocompromised patients receiving suppressive therapy. Persistent or recurrent lesions during treatment should prompt susceptibility testing of viral isolates, although recurrence of outbreaks does not warrant cessation of suppressive therapy. Acyclovir-resistant HSV is also resistant to valacyclovir and usually is resistant to famciclovir. Alternatives include foscarnet (40 mg/kg IV every 8 hours) or cidofovir gel 1% (daily for 5 days).

Screening for Gonococcal and Chlamydial Infections

Screening for *Chlamydia trachomatis* infection in women can be performed with nucleic acid amplification tests on endocervical swabs or urine specimens. Nucleic acid amplification tests on urine offer ease of sample collection as well as comparable sensitivity to that of the same test performed on endocervical samples. Alternative tests consist of DNA probes, enzyme immunoassay, or direct fluorescent antibody (DFA) testing on endocervical swab specimens or culture of endocervical specimens. These tests are less sensitive than nucleic acid amplification tests but may offer improved specificity. Screening for gonorrhea using endocervical swab specimens should be performed by culture due to the continuing need for antimicrobial-resistance monitoring. If culture is not available, nucleic acid amplification or DNA probe testing of endocervical specimens can be performed. Nucleic acid amplification tests can be used for urine specimens and offer similar benefits to that of chlamydia testing. Similarly, in screening for urethral chlamydial infections in men, it is recommended that nucleic acid amplification tests be used on urethral or urine specimens. Alternatively, non-nucleic acid amplification tests or culture can be used on urethral specimens. For gonococcal infection, culture of urethral swab specimens is recommended, with use of nucleic acid amplification tests or DNA probes on urethral specimens or nucleic acid amplification tests on urine specimens constituting alternative methods.

Rates of *Neisseria gonorrhoeae* resistance to fluoroquinolones, which constitute standard treatment for gonorrhea, are increasing in many locales. Data from the Gonococcal Isolate Surveillance Project indicate a steady increase in proportion of strains with resistance or decreased susceptibility to ciprofloxacin between 1996 and 2000 (Figure 1). There is, however, significant geographic variation in resistance. In most of the United States, strains of *N. gonorrhoeae* remain susceptible to fluoroquinolones. Increasing fluoroquinolone resistance rates are reported in Southeast Asia, the Pacific Islands, and in Hawaii and California in the United States; current STD treatment guidelines recommend fluoroquinolone treatment not be used for gonorrhea in California and Hawaii. Thus far, no gonococcal resistance to ceftriaxone has been reported.

HIV-infected women and men can be screened for pharyngeal and rectal chlamydial and gonococcal infections. For chlamydial infection, pharyngeal or rectal culture (or DFA, using a *C. trachomatis* major outer membrane protein-specific stain may be acceptable as an alternative) can be used. For gonococcal infection, culture with additional testing of presumptively positive colonies (ie, typical morphology, oxidase-positive, Gram-negative diplococci) can be performed.

Syphilis

Of the more than 700 cases of syphilis reported in Los Angeles in 2002, approximately 70% occurred in MSM; of those, approximately 60% occurred in MSM with HIV infection (Figure 2). These data strongly indicate that some subgroups of MSM, including those with HIV disease, are engaging in high-risk sexual behaviors and suggest the potential for an increase in incidence of HIV infection. Indeed, preliminary data from the Los Angeles County Office of AIDS Programs and Policy indicate a rising incidence of HIV infection among MSM in Los Angeles. It is unclear the extent to which the syphilis epidemic in Los Angeles has contributed to the projected increase in incidence among MSM; nevertheless, heightened attention to screening for syphilis is warranted.

Numerous treatment regimens for syphilis are available. Data on treatment success in HIV-infected patients are conflicting, and there are some data indicating that HIV-infected patients progress more rapidly through stages of

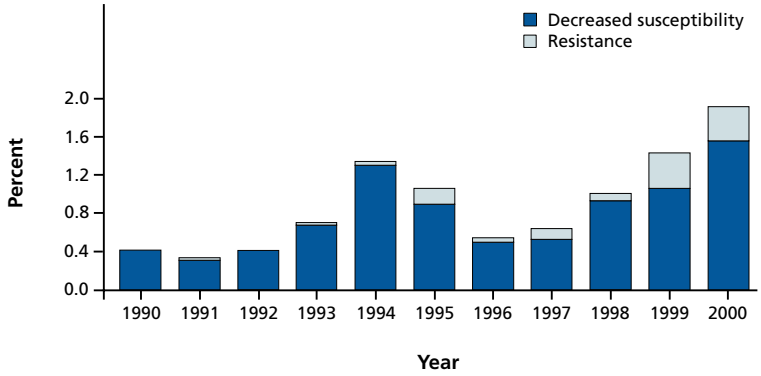

Figure **1.** Percent of *Neisseria gonorrhoeae* isolates with decreased susceptibility (minimum inhibitory concentrations 0.125 to 0.5 µg/mL) or resistance (minimum inhibitory concentrations ≥1 µg/mL) to ciprofloxacin, according to the Gonococcal Isolate Surveillance Project. Adapted from materials from the Centers for Disease Control and Prevention. Available at www.cdc.gov/std/gisp/.

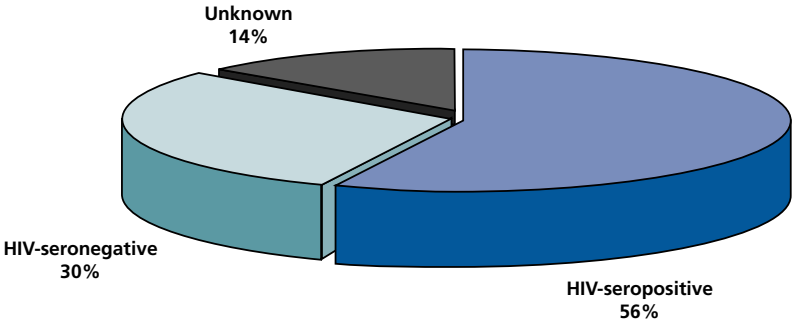

Figure **2.** HIV serostatus in 406 cases of syphilis among men who have sex with men in Los Angeles County in 2002 (provisional data). Adapted from Sexually Transmitted Disease Program, Los Angeles County Department of Health Services, Early Syphilis Surveillance Summary, 2003.

syphilis than do patients without HIV infection. Thus, rigorous follow-up of HIV-infected patients is required regardless of the chosen treatment regimen. Repeated serologies are necessary to ensure that treatment has been successful. If initial treatment is not successful, patients should undergo workup for neurosyphilis and treatment should be repeated.

In most HIV-infected patients, primary, secondary, and early latent (< 1 year of exposure), syphilis responds appropriately to benzathine penicillin 2.4 mU intramuscularly (IM) times 1 dose. Benzathine penicillin should not be confused with Bicillin formulations (containing short-acting procaine penicillin) that are not appropriate for use in treating persons with syphilis. Some experts recommend performing cerebrospinal fluid (CSF) examination prior to therapy, and if CSF is normal, providing additional treatment—eg, weekly benzathine penicillin IM for 3 weeks—in HIV-infected patients. Clinical and serologic evaluation should be performed at 3, 6, 9, 12, and 24 months after treatment, with some experts performing CSF examination at 6 months. Those patients with clinical or serologic failure (eg, the absence of a 4-fold decline in serum RPR titer) at 6 to 12 months after initial treatment should undergo CSF examination and be retreated with benzathine penicillin 2.4 mU IM weekly for 3 weeks in the absence of neurosyphilis.

HIV-seropositive patients with late latent syphilis (> 1 year of exposure) or syphilis of unknown duration should undergo CSF examination before treatment. Those with normal CSF results should receive benzathine penicillin 2.4 mU IM weekly for 3 weeks and undergo clinical and serologic evaluation at 6, 12, 18, and 24 months after treatment. CSF examination and treatment should be repeated if symptoms develop or if a rise of 4-fold or greater in antibody titer is observed. CSF examination and treatment should also be repeated if the nontreponemal antibody test titer does not decline within 12 to 24 months. Diagnosis of neurosyphilis is based on CSF white blood cell count and protein levels and a positive non-treponemal (usually Venereal Disease Research Laboratory, VDRL) test performed on CSF. Sensitivity in diagnosis can be improved with use of fluorescent treponemal antibody absorbption (FTA-ABS) testing on CSF, although false-positive findings occur with this method when CSF is contaminated with blood. Diagnosis presents some difficulty in the case of HIV-infected patients with negative CSF-VDRL results, since HIV infection alone is associated with CSF abnormalities, including pleocytosis and elevated protein, in approximately 30% of patients. A high index of suspicion for neurosyphilis should be maintained in patients with CSF abnormalities and negative VDRL test results, since many of the neurologic complications of disease can be permanent. The recommended treatment for neurosyphilis is aqueous crystalline penicillin G 18 to 24 mU given at 3 to 4 mU IV every 4 hours for 10 to 14 days. An alternative regimen is procaine penicillin 2.4 mU IM daily plus probenecid 500 mg orally 4 times daily for 10 to 14 days. Some experts also recommend treatment with benzathine penicillin 2.4 mU IM weekly for 3 weeks following completion of these regimens to provide duration of treatment comparable to that for latent syphilis. Recent experience indicates that treatment with ceftriaxone 2 g IV for 10 to 14 days may be effective in treating neurosyphilis, as well. As is true for other HIV-infected patients with syphilis, patients receiving treatment for neurosyphilis should be followed closely after treatment to ensure treatment success.

HPV Infection

Women with HIV infection should be screened for cervical cancer associated with HPV infection. There is an increased prevalence of squamous intraepithelial lesions in HIV-infected women. Pap testing should be performed in all women twice in the first year of HIV infection diagnosis and annually thereafter if initial findings are normal. Management in the case of abnormal findings on Pap testing should follow the Interim Guidelines for Management of Abnormal Cervical Cytology provided by a National Cancer Institute Consensus Panel (Kurman et al, *JAMA*, 1994). Women with high-grade squamous intraepithelial lesions or squamous cell carcinoma with cytology should be referred for colposcopy and biopsy.

In men, HPV types 16 and 18 account for the majority of HPV infections in the anal canal and the majority of cases of anal intraepithelial neoplasia, which is a precursor to anal squamous cell cancer. The prevalence of anal intraepithelial neoplasia increases with decreasing CD4+ cell count in HIV-infected men. Although anal Pap testing is very sensitive in detecting such neoplasia, therapeutic strategies remain undefined due to an absence of sufficient data on treatment (Mathews, *Top HIV Med,* 2003). Thus, the Centers for Disease Control and Prevention currently does not have a recommendation

with regard to routine screening. More frequent biopsies may be considered in patients with recurrent lesions because of the increased risk of progression with recurrence. Currently, only local therapies applied by the patient or health care provider are recommended.

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Suggested Reading

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