Perspective

Sexually Transmitted Infections and HIV: Epidemiology and Interventions

Although the association of HIV and sexually transmitted infections (STIs) has been well known for 25 years, there is insufficient attention to STIs by many HIV providers, in part because patients are asymptomatic or have nonspecific symptoms and because of provider demands and focus. Optimal patient care requires frequent testing for STIs as well as obtaining an accurate medical history, which requires building trust with patients and asking direct but open-ended questions about risks and symptoms. Increased vigilance will also help practitioners avoid missing these infections. Herpes simplex virus type 2 infection has highly variable clinical manifestations, and diagnosis is needed before considering episodic or suppressive treatment. However, suppressive treatment of herpes simplex virus type 2 infection has not been shown to reduce risk of HIV acquisition. The increase in syphilis rates continues; screening is inexpensive and treatment is highly effective. Quinolone resistance rates in gonorrhea are increasing, complicating treatment in some locales. Cases of proctitis caused by chlamydial infection with lymphogranuloma venereum strains have been observed in the United States and Europe. This article is a summary of a presentation by Connie L. Celum, MD, MPH, at the International AIDS Society–USA continuing medical education program held in March 2010 in New York City.

Sexually transmitted infections (STIs) are commonly underdiagnosed by HIV care practitioners. Thus, it is important to increase vigilance and recognize that STIs are often asymptomatic or have nonspecific symptoms, that their presence can increase HIV infectiousness, and that regular testing for STIs is needed to ensure optimal treatment of HIV-infected patients.

Herpes Simplex Virus Type 2 Infection

Twenty years' worth of epidemiologic data support a synergistic relationship between herpes simplex virus type 2 (HSV-2) and HIV infections. Reactivation of HSV-2 increases HIV susceptibility and infectiousness and potentially accelerates HIV disease progression. Also, HIV infection increases the frequency of HSV-2 outbreaks, facilitating HSV-2 transmission. Numerous longitudinal studies that were adjusted for age and sexual behavior have shown that prevalent HSV-2 infection is associated with a statistically significant increase in the relative risk (RR) of HIV acquisition in men (RR, 2.7), women (RR, 3.1), and men who have sex with men (MSM; RR, 1.7). The risk of HIV acquisition appears to be even higher in patients with incident (recently acquired) HSV-2 infection (RR, ~6), although it is difficult to discern whether individuals acquired HSV-2 infection before or at the same time as HIV infection. In some African locales where HSV-2 prevalence is very high, mathematical modeling and epidemiologic analyses estimate that up to one-third to one-half of new HIV infections can be attributed to HSV-2 infection.

Biological plausibility for increased HIV susceptibility comes from various lines of evidence. These include studies showing that HSV-2 causes macroscopic and microscopic ulcerations and that HSV-2 reactivation is quite frequent. Studies of HIV-seronegative persons in which patient-obtained genital swabs were tested by HSV polymerase chain reaction show that reactivation occurs on 20% of days and even more frequently if HSV shedding is evaluated more than once daily (Mark et al, *J Infect Dis*, 2008). Also, HSV-2-infected women who were not necessarily shedding virus had increased populations of HIV target cells, specifically immature dendritic cells and cervical CD4+ T cells expressing CC chemokine receptor 5 (CCR5) (Rebbapragada et al, *AIDS*, 2007).

Such data provided the rationale for investigating whether suppression of HSV-2 could reduce acquisition of HIV. In a placebo-controlled study in 821 HSV-2-seropositive, HIV-seronegative Tanzanian women at high risk of HIV infection—a study in which the drop-out rate was high, adherence was modest, and clinic visits occurred only quarterly—twice-daily acyclovir 400 mg showed no effect in preventing HIV acquisition (Watson-Jones et al, *N Engl J Med*, 2008). Another trial conducted with the same acyclovir dose in more than 3000 HSV-2-seropositive, HIV-seronegative women in African locales and MSM in Peru and the United States also showed no preventive effect in HIV acquisition (Celum et al, *Lancet*, 2008).

A potential explanation for why HSV-2 suppression did not reduce risk of HIV acquisition is provided by recent data supporting a "sparks-and-embers" model of continued susceptibility even in patients with suppressed HSV-2 outbreaks. These data show that as the host genital mucosal immune system persistently encounters HSV-2 antigen, localized persistence of CCR5+ cells is imprinted in genital skin and mucosa, resulting in a 10-fold increase in CD4+ cells and dendritic cells in the genital epithelium that lasts for more than 8 weeks after HSV-2 reactivation (Zhu et al, *Nat Med*, 2009). The increased infiltration of HIV target

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cells ("sparks") and increased local enhancement ("embers") provides HIV with an advantage in an initial contact between HIV and host. Although current HSV-2 drugs can suppress reactivation, they do not reduce the persistent inflammation of the genital mucosal HIV target cells. Thus, the susceptibility to HIV acquisition remains increased.

Other studies have evaluated whether suppression of HSV-2 in patients coinfected with HIV can reduce HIV infectiousness or HIV disease progression. The plausibility of such effects is supported by a number of findings. First, data from the pre–potent antiretroviral therapy era indicated that the addition of high-dose acyclovir to nucleoside analogue reverse transcriptase inhibitor (nRTI) treatment improved survival. Second, HSV-2 reactivation is more frequent in HIV-infected persons than in uninfected persons. Lesions persist longer and high amounts of HIV RNA are present in lesion fluid (exceeding plasma levels). Third, increased levels of plasma and genital HIV RNA are present during even asymptomatic HSV-2 reactivation. Fourth, HSV proteins produced during reactivation have been demonstrated to upregulate HIV replication in vitro. Finally, numerous studies (generally small and with short follow-up periods) have shown that in HIV-infected persons with CD4+ cell counts greater than 250/μL who are not receiving antiretroviral therapy, acyclovir or valacyclovir suppressive therapy is associated with reductions in HIV RNA levels in plasma (by 0.3 $\log_{10}$–0.5 $\log_{10}$ copies/mL) and in rectal, seminal, and cervical secretions.

In the recent Partners in Prevention HIV and HSV transmission study conducted in 7 countries in Africa, each HIV- and HSV-2-coinfected person in 3400 HIV-serodiscordant couples was randomly assigned to receive twice-daily acyclovir 400 mg or placebo, and the couples were observed for up to 2 years (Celum et al, *N Engl J Med*, 2010; Lingappa et al, *Lancet*, 2010). The HIV-infected partners had CD4+ cell counts of 250/μL or greater (the national guidelines threshold for initiating antiretroviral therapy) and were not receiving antiretroviral therapy at study entry. Over the 2 years, acyclovir treatment was not associated with a statistically significant prevention of HIV acquisition (hazard ratio, 0.92; 95% confidence interval, 0.60–1.41; $P = .69$), despite a 0.25 $\log_{10}$ copies/mL reduction in plasma HIV RNA level and a 0.75 $\log_{10}$ copies/mL reduction in genital ulcer secretions. However, acyclovir suppression was associated with a statistically significant 16% reduction in HIV disease progression measured as the composite of decrease in CD4+ cell count to less than 250/μL, initiation of antiretroviral treatment, or death. Treatment was also associated with a statistically significant 19% reduction in progression to CD4+ cell counts of less than 350/μL in patients entering the study with counts above this level.

The lessons learned from the recent intervention studies include the following: a suppressive regimen (twice-daily acyclovir 400 mg) does not resolve persistent inflammation caused by HSV infection; such suppressive treatment does not prevent HIV transmission despite reductions in HSV-2 outbreaks and a 0.25 $\log_{10}$ copies/mL reduction in plasma HIV RNA levels; and twice-daily acyclovir 400 mg modestly reduces progression of HIV disease in patients not receiving antiretroviral therapy who have CD4+ cell counts of 250/μL or greater.

One conclusion is that for patients coinfected with HIV and HSV-2, practitioners could consider initiating antiretroviral therapy earlier for those with CD4+ cell counts greater than 350/μL to reduce their likelihood of HIV transmission and for clinical benefits. Another conclusion is that further consideration should be made of the potential use of HSV-2 suppressive treatment in coinfected patients with CD4+ cell counts greater than 350/μL who are not eligible for or who elect not to initiate antiretroviral therapy. A third conclusion is that more effective drugs for HSV-2 infection are needed, as is a genital herpes vaccine. Unfortunately, the recently released results of the Herpevac Trial for Women (cosponsored by the National Institute of Allergy and Infectious Diseases and GlaxoSmithKline) of a candidate HSV-2 vaccine in HSV-1- and HSV-2-seronegative women showed no efficacy, and the pipeline for other HSV-2 vaccine candidates is limited.

The interaction of HSV-2 and HIV infections emphasizes the importance of genital herpes testing and appropriate counseling. Type-specific HSV-2 serology tests may be useful for patients with recurrent and atypical symptoms and negative culture results, for patients with a clinical diagnosis of HSV-2 but no laboratory confirmation, and for patients with a sexual partner with genital HSV infection. Type-specific testing might also be appropriate for patients presenting for comprehensive STI evaluation, for those with HIV infection or several sexual partners, and for MSM with high risk of acquiring HIV. Type-specific enzyme immunoassays (EIAs) for HSV-2 have sensitivity and specificity of 97%, and results can be expected to become positive within 3 weeks after the acquisition of HSV-2 infection. Updated STI guidelines are expected soon from the US Centers for Disease Control and Prevention (CDC) regarding recommendations for serologic testing for HIV-infected patients and for those with high-risk behaviors for HIV acquisition.

Syphilis

The recent increase in incidence of syphilis shows no sign of slowing. Increased syphilis rates have been observed in the last 7 consecutive years for which there are data (Figure 1). Currently, rates are 6 times higher in men than women and 7 times higher in blacks than whites; approximately two-thirds of cases are in MSM, many of whom are coinfected with HIV. Regarding risk factors for HIV-1 acquisition, the data for early syphilis and other non-HSV causes of genital ulcer disease are less clear and consistent than are the data for HSV-2 causes. However, there is an ongoing epidemic of primary and secondary syphilis among MSM in US cities and some European cities, with a majority of cases identified among HIV-infected MSM. Given that serologic screening is sim-

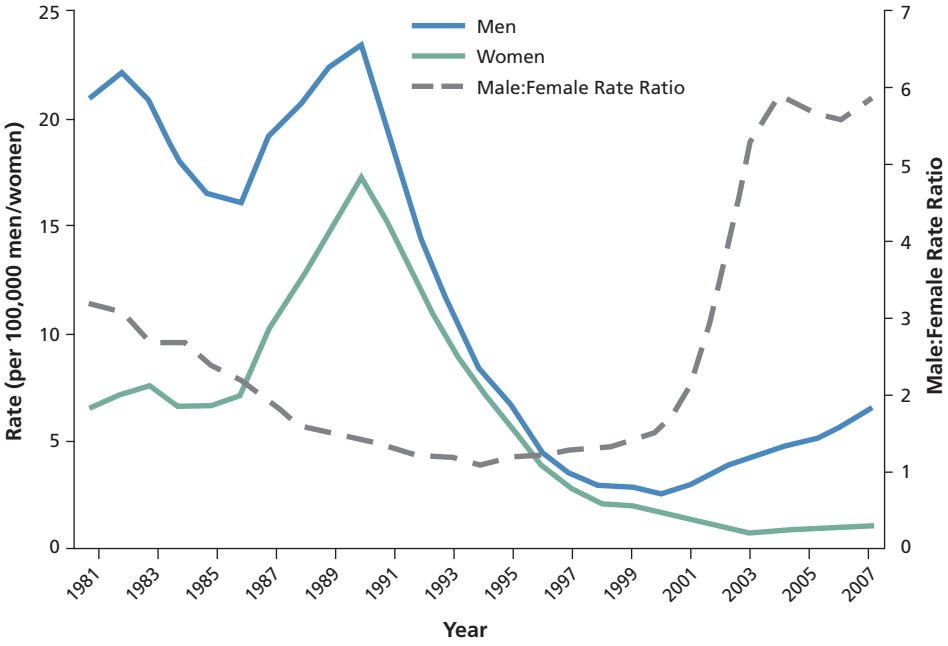

Figure **1.** Rates of primary and secondary syphilis in the United States through 2007. Adapted from Centers for Disease Control and Prevention and US Department of Health and Human Services, 2009.

ple and reliable and syphilis is readily treatable, HIV practitioners must be vigilant in conducting serologic screening for syphilis and treating syphilis in HIV-infected MSM.

Because of these increasing syphilis rates, the importance of screening and recognizing the early clinical manifestations of syphilis needs to be reemphasized. Even in locales with outbreaks, individual practitioners may see few cases, and syphilis manifestations are easily misdiagnosed. For example, primary syphilis chancres may have unusual presentations and may be asymptomatic. Secondary syphilis rashes can mimic a wide range of conditions. In approximately 60% of cases, secondary syphilis involves the palms or soles of the feet. Although practitioners are frequently taught to examine the hands and palms first, rash often begins on the trunk and moves peripherally. Rash usually is not pruritic or vesicular and may be subtle or widespread and florid. The mouth and genitals should also be examined because some cases of secondary syphilis present as mucous patches on the tongue or as condyloma lata. Occasionally, patients with secondary syphilis exhibit hepatosplenomegaly, alopecia, and other nongenital manifestations.

The differential diagnosis of syphilis includes rash associated with antiretroviral therapy, tinea versicolor, pityriasis rosea, generalized scabies, fixed drug eruption, erythema multiforme, and psoriasis. It is important to maintain a high degree of suspicion for syphilis and to order serologic testing for asymptomatic patients. Titers should be monitored for 6 months to 12 months for patients with primary or secondary syphilis, as titers may persist at higher levels than previously thought.

Most syphilis is diagnosed through serologic screening. The new screening paradigm is to first use treponemal tests (ie, EIAs or chemiluminescence immunoassays specific to *Treponema pallidum*). Such assays provide qualitative results and reactivity that persists over a lifetime. Nontreponemal (eg, rapid plasma reagin [RPR] and VDRL) tests are then used to obtain quantitative results necessary for clinical management. The treponemal tests are highly automated, less costly, and easier to perform than the nontreponemal tests. However, false-positive results can occur with treponemal tests, presenting diagnostic challenges in low-prevalence populations.

Latent syphilis is divided into early latent (< 1 year) or late latent (> 1 year) syphilis for treatment purposes. Syphilis of unknown duration is managed the same way as late latent syphilis. Latent syphilis is diagnosed according to symptoms and history of test results. If a patient undergoes annual testing and a positive test result occurs at some point, a diagnosis of early latent disease can be made comfortably. Criteria for early latent syphilis include negative serology results in the past year, known exposure to someone with an early case of syphilis, clear history of typical signs and symptoms in the past year, positive serology results in a patient whose only exposure came within the past year, and a 4-fold increase in titer in the past year. The last criterion might also indicate treatment failure and may provide rationale for performing lumbar puncture (LP).

The decision to perform LP for examination of cerebrospinal fluid (CSF) in latent syphilis is fairly straightforward for patients with neurologic or ophthalmic signs or symptoms, evidence of tertiary disease (gumma, aortitis), or treatment failure (eg, 4-fold rise in titers). In patients with HIV infection, CSF examination should also be performed in those with late latent syphilis or latent disease of unknown duration in the presence of neurologic symptoms. LP should also be considered in HIV-infected patients with syphilis at any stage and CD4+ cell counts of 350/μL or less and RPR titer greater than or equal to 1:32. Diagnostic specificity for asymptomatic neurosyphilis is improved by using a CSF pleocytosis cutoff value of greater than 20 white blood cells/mL. Recent data indicate that in immunocompetent patients—eg, HIV-infected patients receiving antiretroviral therapy—normalization of serum RPR titer is predictive of normalization of CSF parameters, which may reduce the frequency needed for follow-up LPs.

Treatment of primary, secondary, or early latent syphilis in adults is with long-acting penicillin G benzathine (2.4 million units, single-dose

intramuscular injection). No data support benefits of higher doses, additional doses, or longer treatment with penicillin G benzathine, amoxicillin, or other antibiotics. Other treatment options (eg, for nonpregnant, penicillin-allergic adults) include oral doxycycline (100 mg twice daily for 2 weeks), oral tetracycline (500 mg 4 times daily for 2 weeks), and intravenous or intramuscular injections of ceftriaxone (1 g daily for 10–14 days). When possible, it is preferable to avoid the doxycycline and tetracycline regimens, given the importance of patient adherence. Oral azithromycin (2 g, single dose) is also an option, although most practitioners currently recommend avoiding it (and not using it for MSM or pregnant women) because of recent data suggesting problems with drug resistance.

Gonorrhea

The major new concern in gonorrhea management is the emergence of quinolone resistance. The new nucleic acid amplification tests (NAATs) work well for diagnosis but do not identify antibiotic resistance. The potential presence of quinolone-resistant infection in patients who have traveled to locales with high rates of quinolone resistance or who are not responding to quinolone therapy should prompt the order of a culture. Routine annual screening of exposed sites—eg, urethra, pharynx, and rectum—should be performed. Retesting should be performed after treatment.

Recommended treatment is cefixime (oral, 400 mg) or ceftriaxone (intramuscular injection, 250 mg). Other treatment options include oral cefpodoxime (400 mg), oral cefuroxime (1 g), and single-dose injectable cephalosporin regimens. Single-dose oral quinolone regimens are also an option, although many practitioners avoid using quinolones because of the increasing problem with resistance. Patients should be treated empirically and concurrently for chlamydial infection, unless it is ruled out by results from a highly sensitive test (ie, NAAT).

Treatment options for cephalosporin-allergic patients have become more limited since the removal of spectinomycin from the US market. The CDC currently recommends allergy desensitization procedures but recognizes this is not possible for many patients. A regimen of 2 g of azithromycin can be considered, but patients need to be prepared for the gastrointestinal side effects associated with this dose. Further, resistance to azithromycin is increasing, and treatment failures have been observed. If possible, cultures to determine drug sensitivity should be performed before treatment; if not, test-of-cure procedures should be performed at 3 days to 5 days by culture or at 3 weeks by NAAT. Some locales still have low rates of quinolone resistance associated with gonorrhea, thus practitioners need to stay abreast of the local epidemiology and upcoming CDC STI treatment guidelines.

Proctitis

The differential diagnosis of proctitis includes HSV infection (typically, primary episode), gonorrhea, and *Chlamydia trachomatis* infection, including infection with strains that cause lymphogranuloma venereum (LGV). LGV is frequently associated with inguinal lymphadenopathy (buboes) and genital ulcer. Characteristics of recent cases of LGV proctitis in the United States include a tendency for delayed diagnosis and presentations typically occurring in HIV-infected MSM with a history of unprotected receptive anal sex. Practitioners should consider ordering cultures for *C trachomatis* rather than using NAAT for diagnosing proctitis in such patients.

The treatment recommendations for uncomplicated chlamydial infection are azithromycin (1 g single dose) and doxycycline (100 mg twice daily for 7 days). Alternative treatment options include erythromycin (base, 500 mg 4 times daily for 7 days), erythromycin succinate (800 mg 4 times daily for 7 days), ofloxacin (300 mg twice daily for 7 days), or levofloxacin (500 mg daily for 7 days). These regimens are 97% to 98% effective, generally eliminating the need for test-of-cure procedures. For patients with LGV, doxycycline must be administered for 3 weeks instead of 7 days.

Human Papillomavirus Infection

Human papillomavirus (HPV) DNA testing is clinically useful for triage of Papanicolaou smears indicating atypical squamous cells of undetermined significance in women more than 20 years old and for adjunctive screening in women 30 or more years old. It has no proven benefit in deciding whether to provide HPV vaccination, STI screening, triage of low-grade squamous intraepithelial lesions or of higher-grade lesions in adults, testing of adolescents younger than 21 years old, evaluation of sexual partners, or evaluation of genital warts.

The HPV vaccine is recommended in girls and women aged 9 years to 26 years for prevention of cervical cancer, genital warts, and precancerous lesions of the cervix, vagina, and vulva. Available data indicate that the vaccine has no preventive effect in women already infected with HPV. The vaccine has been shown in ongoing trials to be safe and immunogenic in HIV-infected women; however, most HIV-infected women already have HPV infection. Data for HIV-seronegative men indicate efficacy of the vaccine in preventing genital warts and precancerous lesions; an advisory panel of the US Food and Drug Administration recommended approval of the vaccine in such patients.

Screening and Prevention

The primary principles of evaluating patients for STIs are that practitioners need to actively examine patients for signs and symptoms and elicit full histories from their patients. For preventive efforts to be successful, patient sexual history must be obtained routinely, and patients must be counseled regularly about risk reduction. Screening is crucial because so many conditions are asymptomatic. Patients should be informed about which STIs they are tested for and which not; too often, patients assume they have had a negative result for a test that was

never performed. Patient history about behaviors and anatomic sites of exposure should guide the selection and frequency of screening tests. For MSM, screening should include serologic testing for HIV after oral or anal exposure, syphilis after any unprotected exposure, HSV-2 at initial evaluation, gonorrhea and chlamydial infection in the urethra or in urine after oral or anal exposure and in the rectum after receptive anal intercourse, and gonorrhea in the pharynx after receptive oral intercourse. Testing should be done at least annually and more frequently in patients with increased risk.

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Suggested Reading

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