Perspective

Sexually Transmitted Infections in the Context of HIV Disease: Clinical Implications

Universal screening and frequent retesting are required to reduce the burden of sexually transmitted infections in the HIV-infected population. Dual treatment is available for gonorrhea, expedited partner therapy is effective and legal in most states, sexually transmitted infection rates are high in the context of preexposure prophylaxis, and there is a continuing rise in rates of syphilis, particularly early neurosyphilis. This article summarizes a presentation by Dana W. Dunne, MD, FACP, at the IAS–USA continuing education program, Improving the Management of HIV Disease*, held in New York, New York, in March 2016.*

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Clinicians must be highly vigilant regarding sexually transmitted infections (STIs). HIV incidence remains high, and STIs indicate high-risk behaviors and increase the risk of HIV transmission, which represents an individual and a public health concern. The goal of reaching zero HIV transmissions requires more-effective STI screening and treatment of HIV-infected individuals.

To illustrate the relevance and practical points of STI testing and treatment in this population, the case of the following typical patient will be presented throughout.

Case: *A 40-year-old man with well-controlled HIV infection who describes himself as bisexual and is currently in a relationship with an HIV-seropositive woman presents for care. He has no symptoms.*

Common questions practitioners ask in such a case are: 1) if STI rates are high enough after initial clinic intake to warrant continued screening; 2) if screening can be limited to exposed anatomic areas; and 3) if a urine sample alone is enough.

STI rates are high in HIV clinics. In a study based in HIV primary care clinics in 4 large US cities, approximately 13% of participants had STIs at the time of enrollment, and the incidence of new STIs at 6 months was 7%. Men who have sex with men (MSM) accounted for 94% of STIs (excluding trichomoniasis) and 20% of incident infections at 6 months. The most common STIs were rectal *Chlamydia trachomatis* and pharyngeal gonococcal infections. Rates of screening were suboptimal, with only 39% of HIV-infected individuals screened for *C trachomatis* and gonococcal infections and only 10% of MSM screened at extragenital sites.[1,2]

Thus, it is important to remember the principles of routine STI testing in the era of HIV disease. The initial visit to establish care should include a syphilis serology, nucleic acid amplification tests (NAATs) for *C trachomatis* and gonococcal infections at exposed sites, testing for trichomoniasis (via NAAT or antigen detection) and cervical Papanicolaou testing for women, and testing for hepatitis A, B, and C virus infections. More-frequent testing should be performed based on risk behaviors, including for individuals with a new sex partner, a partner who has concurrent partners, more than 1 partner, or a partner who engages in behaviors that put them at high risk for STIs.

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Screening: Where and What

Data indicate that selective screening or screening based on symptoms can miss up to half of STIs[3] and that screening urine only misses the majority of STIs in MSM.[4] Thus, universal STI screening should be performed every 3 to 6 months for at-risk individuals regardless of symptoms or of site exposed. Screening should include urine and rectal NAATs for *C trachomatis* and gonococcal infections and a pharyngeal NAAT for gonococcal infection, as well as syphilis serology. In male genital testing, first void urine is as effective as endourethral swabbing. For women, urine testing is typically less sensitive than vaginal swabbing, which is slightly more sensitive than endocervical swabbing; swabs can be practitioner or patient collected. For extragenital testing, individuals should undergo pharyngeal and rectal swabbing, and samples may be practitioner or patient collected.

Case cont.: *STI screening results are returned. The patient has pharyngeal gonorrhea, but chlamydia testing results at all anatomic sites (using NAATs) are negative.*

Dual Treatment for Gonorrhea

The Centers for Disease Control and Prevention (CDC) recommends that dual therapy with a single dose each of ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally be used for treatment of uncomplicated genital, rectal, or pharyngeal gonorrhea.[5] Azithromycin should be used in this setting regardless of *C trachomatis* test results. Dual therapy is advocated by the CDC as a strategy to hinder emergence of antimicrobial resistance. If ceftriaxone is unavailable, a single dose of cefixime 400 mg orally may be substituted for treatment of anorectal infection. If cefixime is used for pharyngeal infection, it must be accompanied by a test of cure in 2 weeks. Azithromycin 2 g is no longer recommended as an alternative treatment for individuals who are allergic to cephalosporins, owing to concern about emerging macrolide resistance.

To break the cycle of reinfection, retesting for STIs is crucial. Women with *C trachomatis* infection, gonococcal

infection, or trichomoniasis, and men with *C trachomatis* or gonococcal infection should be rescreened at 3 months after treatment. Individuals diagnosed with syphilis should undergo follow-up serology per current recommendations.[5] Retesting is not the same as a test of cure but, rather, acts as a surrogate for assessing whether sex partners have also been treated.

Case cont.: *The patient is informed about his gonococcal pharyngitis and is treated with ceftriaxone and azithromycin. The clinician should now consider partner notification and treatment.*

Expedited Partner Therapy

Expedited partner therapy (EPT), in which individuals provide medicines to their sex partners (otherwise known as patient-delivered partner therapy) is now permissible in 40 states and "potentially allowable" (subject to additional actions or policies) in 8 states. The only states that currently prohibit EPT are Kentucky and West Virginia (visit the CDC website for frequent updates on the legal status of expedited partner therapy[6]). Studies have demonstrated reduced rates of reinfection in index patients when partners were offered EPT compared with traditional partner referral.[7]

Expedited partner therapy is currently only recommended for heterosexual couples. Because MSM have high rates of undiagnosed HIV infection and syphilis, it is advisable for their sex partners to present to care for a full examination and workup. It should be noted that not every state allows expedited partner therapy for both chlamydia and gonorrhea, as treatment for the latter involves intramuscular ceftriaxone.

Case cont.: *The patient tells his female partner about EPT, but she prefers to visit the clinic. The clinician orders routine STI screening and she is treated, based on her contact with gonorrhea, with ceftriaxone and azithromycin. Her* Trichomonas vaginalis *antigen test result is positive.*

Trichomoniasis: New Tests and Longer Treatment

Microscopy for diagnosis of trichomoniasis is inferior to newer options, including rapid antigen testing and a transcription-mediated amplification *T vaginalis* assay. For transcription-mediated amplification testing for *T vaginalis* infection, the same specimen types used in NAATs for *C trachomatis* and gonococcal infections can be used (ie, vaginal swab, endocervical swab, and urine). Rapid antigen testing is reported to have 90% sensitivity and 100% specificity. Transcription-mediated amplification testing is reported to have 98% sensitivity and 98% specificity.[8] The recommended regimen for trichomoniasis in HIV-infected women is twice-daily metronidazole 500 mg orally for 7 days, with rescreening (ideally with an NAAT) at 3 months.

Case cont.: *The patient advises one of his male sex partners of his STI, and this partner visits the clinic for gonorrhea screening and treatment.*

Screening for Bacterial STIs in a PrEP Clinic

This is an excellent opportunity to screen this partner for chlamydia and gonorrhea at all 3 anatomic sites, perform serologic testing for syphilis and HIV, assess viral hepatitis status, and vaccinate if he is not protected against hepatitis A and B viruses or human papillomavirus (the latter depending on age). This is also an opportunity to discuss preexposure prophylaxis (PrEP) to prevent HIV infection.

Recent studies of PrEP have shown a high burden of bacterial STIs: the PROUD (Preexposure Option for Reducing HIV in the UK) study showed a baseline rate of 63% and an incidence at 6 months of 51% to 57%, the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) study showed a baseline rate of 25% to 31% and a 6-month incidence of 20%, and the Partners PrEP study showed a baseline rate of 10% to 15%.[9,10,11] Accordingly, the CDC provided an interim guideline recommending screening for bacterial STIs every 6 months, including oral and rectal screening.[12] However, more-frequent testing is supported by recent findings. For example, a community PrEP demonstration project in which there was a 21% incidence of STIs in the 6 months prior to initiation of PrEP asked participants about symptoms of STIs along with screening every 3 months. Reliance on symptoms alone to prompt testing would have missed 77% of STIs at 3 months and 68% of STIs at 9 months (Figure 1); repeat patients accounted for the bulk of incident infections.[13] In another study of PrEP among MSM with STIs, at 3 months 90% had engaged in unprotected anal intercourse and had a mean of 3 sex partners.[14] Both studies suggest that, given the high incidence of bacterial STIs in this population receiving PrEP, the currently recommended testing interval of 6 months may result in missed opportunities to mitigate the personal and public health sequelae of untreated STIs.

Case cont.: *A full STI screen and baseline HIV test are performed for the patient's male partner, and he receives treatment for gonorrhea as well as daily PrEP with tenofovir disoproxil fumarate and emtricitabine. He returns for an evaluation 3 months later and STI screening is repeated. He reports blurriness in vision in his left eye. Two days later, his enzyme immunoassay for syphilis returns a positive result, with a reflex rapid plasma regain test result of 1:256. He also reports having a suspicious rash that resolved. His NAAT result for rectal chlamydia is positive.*

Neurologic Complaints and Suspicion of Neurosyphilis

Rates of syphilis continue to increase among MSM. As of 2011, prevalence of primary or secondary syphilis was 2.6% among HIV-seronegative MSM and 10.1% among HIV-seropositive MSM.[15] Data reported in 2014 showed that among MSM with syphilis who attended STI clinics, rates of coinfection with HIV ranged from 10% in Los Angeles, California, to 55% in Philadelphia, Pennsylvania, with intermediate rates in Seattle, Washington; San Francisco, California; Baltimore,

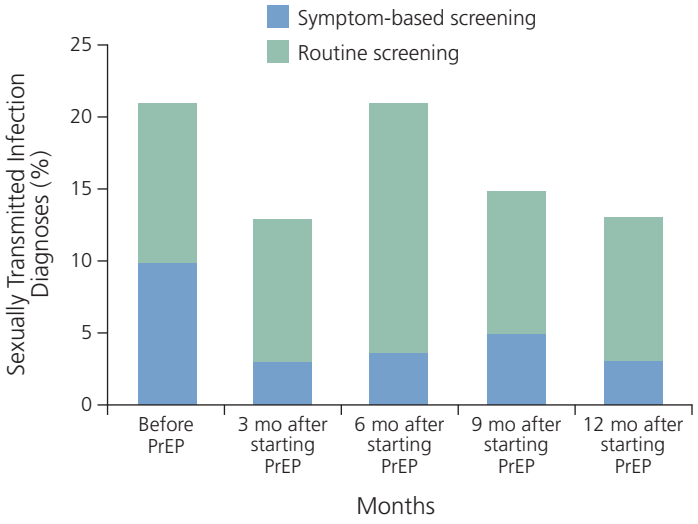

Figure 2. Sexually transmitted infection diagnoses, by time point and routine or symptom-based screening. PrEP indicates preexposure prophylaxis. Adapted with permission from Golub et al.[13]

Maryland; and New York, New York.[16] Because of the synergy between HIV infection and syphilis and the high rates of transmission among MSM, vigilance in screening and disease detection in this population is paramount.

Neurosyphilis can occur at any stage of syphilis infection. The spirochete disseminates through the spinal fluid early on, and early neurologic symptoms can often be seen at the time a syphilis-associated rash appears or shortly thereafter. Symptoms can include visual changes, hearing loss, facial weakness, and those associated with stuttering stroke. Given the rise in cases of syphilis, symptomatic early neurosyphilis (SENS) is seen more frequently. In SENS, ocular manifestations, including uveitis and chorioretinitis, are most common and occur in approximately 50% of cases. Otic manifestations include tinnitus and sensorineural hearing loss. Other early neurologic manifestations include cranial nerve involvement, aseptic meningitis, and stuttering stroke symptoms (meningovascular syphilis). Lumbar puncture is indicated if there are symptoms of neurosyphilis, and if ocular syphilis is suspected, treatment for neurosyphilis should be initiated even if results for neurosyphilis in cerebrospinal fluid are negative.

Practitioners are asked to report cases of ocular syphilis to health departments within 24 hours of diagnosis, given reports of a cluster of cases in California and the Pacific Northwest. The CDC is collaborating with the University of Washington to study *Treponema pallidum* clinical isolates (ocular syphilis in preantibiotic vitreal fluid, cerebrospinal fluid, or blood) to better ascertain whether the increase in reported cases of ocular syphilis is attributable to case-finding bias or to changes in ocular tropism or neurotropism of the spirochete.

Case cont.: *Given his concerning neurologic symptoms (blurriness in left eye) and reactive syphilis serology, a lumbar puncture is performed for the patient's male partner and he is started on treatment for neurosyphilis with high-dose intravenous penicillin G.*

Treatment for Rectal *C trachomatis* Infection

If rectal *C trachomatis* NAAT results are positive in an asymptomatic individual, treatment for uncomplicated *C trachomatis* infection with a single dose of azithromycin 1 g orally or twice-daily doses of doxycycline 100 mg orally for 7 days is appropriate; there is some evidence that doxycycline may be better in this setting, but randomized controlled trials are necessary to definitively answer this question.[17,18] If NAAT results are positive for *C trachomatis* in an individual with symptoms of proctitis, treatment for a presumed lymphogranuloma venereum strain with twice-daily doxycycline 100 mg orally for 21 days is appropriate. Polymerase chain reaction (PCR) testing for lymphogranuloma venereum strains is not currently commercially available.

The male partner referenced above received azithromycin 1 g for his asymptomatic rectal chlamydial infection in addition to a 14-day course of intravenous penicillin for neurosyphilis. His suspected ocular syphilis is reported to the health department. He remains on daily PrEP with tenofovir disoproxil fumarate and emtricitabine and continues to be screened for STIs every 3 months along with his HIV testing and counseling regarding high-risk behaviors.

Online Resources

There are a number of resources for HIV clinicians to access the latest STI testing and treatment recommendations. The CDC offers a free mobile app that provides access to its STI treatment guidelines. The National Network of Sexually Transmitted Disease (STD) Clinical Prevention Training Centers (NNPTC) offers the STD Clinical Consultation Network (STDCCN), an online system that provides free STI clinical consultation services within 1 to 5 business days, depending on urgency, to health care practitioners nationally.[19] Through the STDCCN, practitioners' consultation requests are linked to regional NNPTC STI experts.

Summary

Given the prevalence and the personal and public health ramifications of STIs in HIV-seropositive individuals, it is important to screen individuals for STIs when they visit the HIV clinic. MSM and at-risk heterosexual individuals should be frequently screened at all anatomic sites regardless of symptoms or exposure. Dual treatment with a single dose each of ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally is the recommended treatment for gonorrhea. To ensure that reinfection has not occurred, individuals who test positive for chlamydia, gonorrhea, or trichomonas should be rescreened 3 months after treatment. To help limit the likelihood of reinfection, effective partner notification and treatment strategies are necessary. EPT is effective and is legal in a number of states and should be utilized, although state-by-state recommendations should be reviewed for guidelines regarding target patient populations in which this strategy has been proven safe and effective. Newer testing methods

(eg, NAATs) are available for diagnosis of trichomoniasis and should be used when possible, as better identification of this infection, which is known to increase HIV viral load in cervicovaginal secretions, could play an important role in limiting HIV transmission. STIs are common among individuals taking HIV PrEP and should be screened more often in this setting. Rates of syphilis remain high among MSM, and practitioners should be aware of the neurologic symptoms associated with neurosyphilis. For individuals with rectal *C trachomatis* infection, appropriate treatment should be selected based on the presence or absence of symptoms. Useful online resources to guide STI treatment are now available to practitioners and should be utilized.

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