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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Prevention of Sexually Transmitted Diseases in HIV-Infected Individuals

Laura Quilter[1] · **Shireesha Dhanireddy**[1] · **Jeanne Marrazzo**[2]

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Abstract Prevention of sexually transmitted infections (STIs) is an important part of the care of the HIV-infected individual. STIs have been associated with increased risk of transmission and acquisition of HIV. Among HIV-infected persons, treatment failures and high recurrence rates of some STIs are more common. Despite the recognized importance of prevention and discussion of sexual health, rates of screening for STIs are suboptimal. Moreover, rates of STIs such as syphilis continue to increase particularly in men who have sex with men (MSM). This review focuses on the most common STIs seen among HIV-infected individuals and recommendations for screening and prevention.

Keywords Sexually transmitted diseases · HIV · Gonorrhea · Chlamydia · Syphilis · Hepatitis C

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✉ Laura Quilter
lquilter@uw.edu

Shireesha Dhanireddy
sdhanir@uw.edu

Jeanne Marrazzo
jmm2@uab.edu

[1] Division of Infectious Diseases, Department of Medicine, University of Washington Medical Center, 1959 NE Pacific St, Box 356423, Seattle, WA 98195, USA

[2] Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham School of Medicine, Tinsley Harrison Tower 215 1900 University Blvd., Birmingham, AL 35294, USA

Introduction

As the overall health of persons living with HIV has improved in the last two decades, sexual health, including prevention and detection of STIs, has become an important component of HIV primary care [1]. Evidence is currently insufficient to support that treatment of STIs in HIV-infected persons *directly* reduces HIV infectiousness. However, detection and control of STIs in this population is critical for several reasons, including (1) the likelihood that STIs increase genital HIV load, adequate plasma suppression by antiretroviral therapy notwithstanding, and thus enhance the efficiency of HIV transmission to uninfected sex partners [2]; (2) the opportunity to identify those HIV-infected persons who are engaging in sexual behaviors that efficiently transmit HIV, and thus prioritize prevention interventions for them [3, 4]; and (3) the possibility that HIV seroadaptive practices effectively potentiate the likelihood of STI acquisition in such encounters if condoms are less likely to be used, as some evidence suggests [5].

The annual incidence of STIs in the USA is 20 million, and approximately half of these infections occur in young people aged 15–24. In 2014, 19,999 cases of syphilis were reported, 350,062 cases of gonorrhea, and 1.4 million cases of chlamydia. A recent systematic review of the prevalence of STIs among persons living with HIV demonstrated a mean point prevalence of STI co-infection of 16.3% (SD 16.4, median 12.4%) [2]. STI prevalence was similar for men (13.6%, SD 10.3) and women (15.8%, SD 9.9). Median prevalence of common STIs included syphilis (9.5%), gonorrhea (9.5%), chlamydia (5%), and trichomoniasis (18.8%) [2]. Equally worrisome, recent trends among some HIV infected persons, particularly MSM, indicate a rise in syphilis and gonorrhea [6]; these trends appear to be consistent across different types of settings and locales. As multiple STIs including gonorrhea, trichomoniasis, genital herpes, and syphilis have been

associated with both increased HIV viral replication and genital shedding of HIV, prevention of STIs in HIV-infected individuals results in not only a benefit to the community but to the individual patient as well.

Main

Screening for Common STI in the HIV-Infected Patient

Joint recommendations of the US Centers for Disease Control and Prevention (CDC) and other national organizations, as well as the *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* [7], emphasize the routine assessment of all patients in HIV care settings, at every visit if possible, for risky sexual behaviors and annual screening of all patients for common STIs using the most sensitive tests available [8–10]. For infections of greatest concern, including syphilis, screening every 3–6 months should be considered depending on reported risk. Results of behavioral assessments should direct appropriate screening for common STIs including syphilis, gonorrhea, and chlamydial infection at exposed anatomic sites (pharynx, rectum, and urethra) [10]. Specific details on the assays recommended, and the interpretation of results, can be found at www.cdc.gov/std/treatment.

Despite these recommendations, rates of STI testing in MSM are relatively low, particularly at extra-genital (rectal and pharyngeal) sites. A qualitative study explored provider barriers to testing and found that limited time, inadequate sexual history taking, cultural factors, and confidentiality issues all contributed to suboptimal screening rates [11]. Importantly, patient-related barriers exist as well, including lack of comfort discussing sex with provider and concerns about provider judgment [12].

A risk assessment as part of the sexual history helps identify whether screening should be performed and allows the opportunity to offer risk reduction counseling. Individuals who report having had >10 partners in the last year or anonymous partners, use methamphetamines, have had recent bacterial STI, or have unprotected anal intercourse are considered high risk, and should be tested for STIs every 3–6 months.

Syphilis

Recently published surveillance data from the CDC show that rates of primary and secondary syphilis have doubled since the year 2000, from 2.1/100,000 to 5.3/100,000; the majority of cases are in MSM [13]. Because many syphilis cases are latent (positive serology in the absence of clinical signs), screening HIV-infected patients with serology is critical. Primary care guidelines recommend screening all patients for syphilis upon entry into care for HIV [9]. Common tests include the Venereal Disease Research Laboratory (VDRL) test and the rapid plasma reagin (RPR) test, although enzyme immunoassay (EIA) or chemiluminescent immunoassays (CIA) are increasingly being used. Current enzyme immunoassays include both immunoglobulin M and immunoglobulin G assays [14]. The CDC recommends that syphilis screening can occur with performance first of either a nontreponemal test (e.g., VDRL, RPR) before a treponemal test or with reverse sequence screening, an alternative approach whereby a treponemal immunoassay (EIA or CIA) is performed first, followed by testing of reactive sera with a nontreponemal test [15]. The frequency with which to screen thereafter depends on the patient's sexual risk (see Table 1). Routine serologic screening should be performed at least annually for all sexually active HIV-infected persons, and more frequently (every 3–6 months) for those who are considered high risk. Patients undergoing screening or treatment for syphilis also should be evaluated for all common STIs such as chlamydia and gonorrhea at anatomic sites of exposure .

Hepatitis C

Hepatitis C is a viral hepatitis that affects over three million people in the USA. However, only 50% of those infected have been diagnosed and far fewer (5–6%) have been successfully treated [16].

HCV was long felt to be primarily acquired through receipt of infected blood products, needle sharing, vertical transmission, and unsterile tattoos. However, more recent epidemiologic data show that sexual transmission occurs, particularly among HIV-infected individuals. Approximately 10% of patients with acute hepatitis C reported sexual contact with HCV-infected individuals as their only risk factor [17]. Specific risk behaviors include anal sexual practices that are more likely to traumatize anal mucosa or cause associated bleeding. Unfortunately, no vaccine exists for HCV prevention and unlike hepatitis B, immune globulin is not effective for HCV prevention. Similar to HIV, primary prevention of HCV involves reduction of high-risk behaviors. In addition to sexual risk reduction, individuals with HIV and HCV coinfection should be advised to avoid sharing needles and other drug paraphernalia. Persons co-infected with HCV and HIV should be evaluated for liver disease as they are at risk for accelerated fibrosis and cirrhosis [18].

All patients with HIV should be screened for HCV upon entry into care for HIV. Aside from HCV antibody testing, MSM should be screened with aminotransferase testing. Individuals with elevated alanine transaminase (ALT) should be tested for acute HCV infection with HCV RNA as well as HCV antibody. Studies have demonstrated that up to 16% of HIV-infected patients with established HCV infection with detectable HCV RNA have a negative HCV antibody test [19]. Repeat HCV testing should be considered for MSM

Table 1 STI screening recommendations for HIV-infected individuals

	MSM	High-risk MSM[a]	Women	Heterosexual men
Gonorrhea	Yearly	Every 3–6 months	–	–
Chlamydia	Yearly	Every 3–6 months	Yearly for <25 years of age	–
Syphilis	Yearly	Every 3–6 months	–	–
Trichomonas	–	–	Yearly	–
Hepatitis C	At entry to care	Yearly antibody testing or HCV RNA testing	At entry to care	At entry to care
Hepatitis B	At entry to care	At entry to care	At entry to care	At entry to care

[a] High-risk MSM: >10 partners in a year or anonymous partners, methamphetamine use (patient or patient's partners), recent bacterial STI, or unprotected anal intercourse

who continue to engage in the high-risk sexual practices noted above, but the frequency of screening is unclear [20]. Due to increasing evidence of acute HCV infection acquisition in persons with HIV infection, the 2015 CDC STD Treatment Guidelines recommend that HCV screening be considered at least yearly in those at high risk for infection, especially MSM, and more frequently depending on specific circumstances (e.g., community HCV prevalence and incidence, injection drug use, high-risk sexual behavior, and concomitant STIs) [10]. More frequent screening should particularly be considered in individuals with a history of successfully treated or cleared HCV infection. A study of HIV-infected MSM with a prior history of HCV infection with spontaneous clearance or following successful treatment demonstrated a high rate of HCV re-infection; it has been suggested that such individuals undergo HCV testing for re-infection every 3 to 6 months [21].

Trichomonas

Trichomoniasis is a protozoal infection caused by *Trichomonas vaginalis* that infects the genital tract of both men and women. Women may present with vaginal discharge and men may present with urethritis, but both may also be asymptomatic. *T. vaginalis* affects 3.1% of women of reproductive age. Recent surveillance data showed that the prevalence of *T. vaginalis* in HIV-infected women presenting to an STD Clinic was 29.3%, compared to 6.5% in HIV-uninfected women. Another study in an HIV clinic in Alabama found a prevalence of 17.4%, with African American race being an associated factor for infection [22].

All HIV infected women should be tested at entry to care and subsequently annually for trichomoniasis [23]. Current guidelines also recommend testing asymptomatic and symptomatic HIV-infected women (abnormal vaginal discharge or odor) for *T. vaginalis*. The CDC recommends that women with trichomoniasis should be retested in 3 months, given high rates of repeat infection in this group despite initially adequate response to therapy. Of note, treatment of trichomoniasis may decrease vaginal shedding of HIV [24, 25]. Screening men is not routinely recommended, as urethral prevalence is low in asymptomatic heterosexual men and for MSM, *T. vaginalis* does not infect the oropharynx and rectal prevalence is low [26].

Diagnosis is challenging as the most commonly available test used, saline microscopy, has very low sensitivity, and the infection is commonly asymptomatic, especially in men. The CDC recommends that when possible, more sensitive tests be used; these include direct antigen detection tests or nucleic acid amplification testing (NAAT) [10].

Partner management is not routinely done for most contacts of patients diagnosed with trichomoniasis [27], despite recommendations for partner treatment.

Chlamydia

Chlamydia is one of the most common STIs reported in the USA, likely due to improved widespread screening efforts in young women, as recommended by the US Preventive Services Task Force (USPSTF) and the CDC. Because the majority of infections are asymptomatic, routine screening is key to identification and treatment. All sexually active women under 25 years of age should receive annual testing. Chlamydia screening should be performed on all women and men upon entry into care for HIV and then annually if sexually active.

MSM should be tested more frequently (every 3–6 months) for urethral and rectal infection based on risk. Patients who have tested positive for Chlamydia should be retested in 3 months given high rates of repeat infection after initially successful treatment [10].

Gonorrhea

Rates of antimicrobial resistance to *Neisseria gonorrhoeae* have been increasing over the past two decades. Oral options such as quinolones or cefixime were previously effective treatments for gonorrhea, but increasing rates of resistance, particularly among MSM, have led to parenteral ceftriaxone becoming the drug of choice, with the addition of azithromycin

(regardless of the results of chlamydia diagnostic testing) [28]. For patients with pharyngeal gonorrhea who do not receive a ceftriaxone-containing first-line regimen, a test of cure is recommended 14 days post-treatment. For patients with uncomplicated urogenital or rectal gonorrhea who are treated with the first-line or alternative regimens, a test-of-cure is not needed.

The majority of pharyngeal and rectal gonorrhea is asymptomatic and if only urethral testing was performed, the majority of infections would be missed [29]. Pharyngeal infections are more difficult to treat due to relatively low concentrations of antibiotics in the area.

Nucleic acid amplification testing is preferred due to increased sensitivity compared to culture-based methods, although if there is concern for resistance, then culture and sensitivity is recommended. Gonorrhea screening should be performed on all women and men upon entry into care for HIV and then annually if sexually active. MSM should be tested more frequently (every 3–6 months) for urethral, rectal, and pharyngeal infection based on risk. Patients who have been treated for gonorrhea should be retested 3 months after treatment regardless of whether they believe their sex partners were treated [10].

Hepatitis B

HBV is a sexually transmitted infection but with the introduction of universal vaccination in the USA, prevalence of HBV remains low. All HIV-infected individuals without antecedent immunity or active HBV infection should be vaccinated for hepatitis B and tested for evidence of immunity Table 2 [30]. If testing does not reveal immunity after the first series, repeat vaccination should be considered after immune reconstitution with antiretroviral therapy. A series of double dose vaccine may also be considered [31]. Although immunization is considered the preferred strategy to prevent HBV infection, it has been shown that HBV-active ART (tenofovir, emtricitabine, and/or lamivudine) may decrease the risk of HBV acquisition in nonimmune, HIV-infected individuals [32, 33].

HPV

Human papillomavirus is the most prevalent sexually transmitted infection. Vaccination with HPV quadrivalent vaccine or the HPV 9-valent vaccine is recommended for all HIV-infected individuals, both male and female, between the ages of 9 and 26 (Table 2) [34]. Even patients with known history of HPV infection or cervical or anal dysplasia should still receive immunization. Unfortunately, many patients enter care or are diagnosed with HIV when they are already older than the recommended age of vaccination.

All HIV-infected women should be screened for cervical cancer beginning within 1 year of HIV diagnosis and continue throughout life. Cervical cancer screening guidelines have recently changed to allow less frequent screening for women with previously normal cytology and negative high-risk HPV testing. Detailed guidelines for cervical cancer screening in HIV-infected women can be found at aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

Anal Pap smears should be considered for individuals who practice anal receptive intercourse, have a history of genital warts, and in women with abnormal cervical Pap smears [9]. Despite these recommendations, no long-term data are available to show mortality benefit of performing anal Pap smears.

Genital Herpes

Herpes simplex virus type-2 (HSV-2), the cause of most recurrent genital herpes, is common among HIV-infected individuals with a prevalence of approximately 60–90% [35]. In vitro studies and epidemiologic data strongly support that HSV-2 infection increases transmission of HIV. Suppressive valacyclovir and acyclovir have been demonstrated not only to reduce plasma levels of HIV-1 RNA but also to delay disease progression [36, 37]. Despite this association of HSV and HIV, daily acyclovir suppressive therapy was not shown to reduce risk of HIV transmission in a large clinical trial of over 3000 HIV serodiscordant couples despite a significant reduction in genital ulcer disease [35].

HSV serologies are not routinely recommended for all HIV-infected persons, but can be discussed as an option for

Table 2 Vaccine recommendations for prevention of STIs in HIV-infected individuals

	MSM	Women	Heterosexual men
Hepatitis A	Vaccinate	N/A	N/A
Hepatitis B	Vaccinate if nonimmune	Vaccinate if nonimmune	Vaccinate if nonimmune
HPV	Vaccine age 9–26; Consider anal Pap smears	Vaccinate age 9–26; Cervical cancer screening (Pap +/− HPV co-testing) q1–3 years based on results Consider anal Pap smears if cervical Pap abnormal	Vaccinate age 9–26

patients who do not know their HSV status. For persons who are HSV-negative, condom use and avoiding sexual contact with partners with overt ulcerative lesions are recommended to prevent acquisition of HSV [7].

Prevention with Positives

Every transmission event involves an HIV-infected person. The HIV Prevention Trials Network 052 study and multiple other studies have demonstrated that treatment of the HIV-infected individual reduces transmission to the uninfected sexual partner in serodiscordant couples [38–42]. In HIV-negative partners, the use of pre-exposure prophylaxis (PrEP) with antiretroviral medications has been shown to reduce the acquisition of HIV infection in high-risk patients [43, 44]. The goal of risk reduction counseling and STI screening is to not only improve the health of the HIV-infected individual but to also prevent transmission to others. Targeted prevention messages to HIV-infected individuals, particularly those who are at risk for STIs, should be incorporated into their medical care.

Partner Notification

Reporting STIs to public health for partner notification and treatment is vital to public health and the patient as it serves to prevent reinfection from their sex partners. Moreover, identification of sexual networks will allow for HIV testing of partners of an HIV-infected individual. Expedited partner therapy (EPT) is permissible in most states (www.cdc.gov/std/ept) and allows clinicians to provide either prescriptions or medications for STI treatment to the partners of patients diagnosed with gonorrhea or chlamydia. However, for HIV-infected individuals diagnosed with an STI, reporting to local public health can facilitate HIV and STI testing for the partner.

Conclusion

The prevention and detection of STIs in HIV-infected individuals remain a public health priority and an integral component of HIV primary care. Given the known association between STIs and HIV acquisition and transmission, STI prevention can have an impact on both population-level and individual patient health. With the rise in STI incidence across the USA, particularly syphilis and gonorrhea in MSM, continued STI screening efforts should be directed at HIV-infected individuals.

Compliance with Ethical Standards

Conflict of Interest Laura Quilter, Shireesha Dhanireddy, and Jeanne Marrazzo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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