

Perspective

Sexually Transmitted Infections and HIV: Diagnosis and Treatment

Accurate assessment, diagnosis, and treatment of sexually transmitted infections (STIs) in HIV-infected persons can identify sexual risk behaviors and specific STIs that may increase transmission of STIs and HIV. HIV-infected men and women should be screened annually for syphilis and urogenital gonorrhea and chlamydia. Serologic testing for hepatitis A, B, and C viruses should also be performed. Women should be tested for trichomoniasis and undergo a cervical Papanicolaou test annually. Men who report receptive anal intercourse with men during the preceding year should be screened for rectal gonorrhea and chlamydia. Men who report receptive oral intercourse with men during the preceding year should be screened for oropharyngeal gonorrhea. More frequent screening at 3- to 6-month intervals may be indicated for men who have sex with men who have numerous or anonymous partners. STIs may have unusual presentations in HIV-infected patients. Aspects of diagnosis and management of common STIs will be discussed in this article. This article summarizes a presentation by Kimberly A. Workowski, MD, at the IAS–USA live continuing medical education course held in New York City in October 2011.

Current Guidelines for STI Screening

An accurate risk assessment for sexually transmitted infections (STIs) can identify sexual risk behaviors and specific STIs that may increase the risk of HIV and STI transmission. A crucial component of this evaluation is performing a detailed and accurate history at every visit. A detailed sexual history should include numbers of sexual partners, types of sexual behaviors, previous STIs, condom use, and a review of current symptoms and signs of STIs. Because many STIs are asymptomatic, especially at the pharyngeal and rectal sites, routine screening for curable STIs (syphilis, gonorrhea, chlamydia) should be performed at least annually for all sexually active, HIV-infected persons.

All HIV-infected men and women should be screened annually with syphilis serology and receive urogenital gonococcal and *Chlamydia trachomatis* (GC/CT) testing. Serologic testing for hepatitis A and B viruses, as well as hepatitis C virus (HCV), is also in-

dicated. Women should be tested for trichomoniasis and undergo a cervical Papanicolaou test annually. Men who report receptive anal intercourse with men (regardless of condom use) during the preceding year should be screened for rectal gonorrhea and chlamydia, using a laboratory-validated nucleic acid amplification test (NAAT). Men who report receptive oral intercourse with men during the preceding year should be screened for oropharyngeal gonorrhea using NAAT. Women should be tested for trichomoniasis (using NAAT or culture) and undergo a cervical Papanicolaou test annually. More frequent STI screening (at 3- to 6-month intervals) is indicated for HIV-infected persons who have nu-

merous or anonymous partners, and for those in a geographic area or population with a high prevalence of STIs.

The commercially available GC/CT NAAT tests are not approved by the US Food and Drug Administration (FDA) for use at pharyngeal and rectal sites, but they can be used by laboratories that have met all regulatory requirements for an off-label procedure. Laboratory personnel at the Laboratory Branch of the Division of Sexually Transmitted Diseases (STD) Prevention at the Centers for Disease Control and Prevention (CDC) are also available to help with test validation. Some private health laboratories have validated rectal and pharyngeal testing with NAATs and have specific laboratory ordering and billing codes that may be helpful for providers. Table 1 provides ordering and coding information for these tests.

Identification of an STI is an objective measure of unprotected sexual activity. Accurate diagnosis and effective treatment of STIs is important not only to reduce morbidity for the individual patient and reduce risk of STI transmission, but to also reduce risk of HIV transmission. The CDC STD Surveillance Network can monitor trends in the prevalence of sexually transmitted infections among men who have sex with men attending specific STD clinics within this network (Figure 1).¹

Table 1. Commercial Laboratory Ordering and Billing Codes for Nucleic Acid Amplification Testing

		Ordering Codes for Combined GC/CT NAAT		Ordering Codes for CT-only NAAT
Rectal	LabCorp		Quest	LabCorp
	188672		16506	188706
Pharygeal	188698		70051	188714
	Current Procedural Terminology® Billing Codes			
		CT detection by NAAT: 87491		GC detection by NAAT: 87591

GC indicates *Neisseria gonorrhoeae*; CT, *Chlamydia trachomatis*. For information on specimen collection and transportation, clinicians should contact their local reference laboratory representative.

Dr Workowski is Professor of Medicine in the Division of Infectious Diseases at the Emory University School of Medicine in Atlanta, Georgia.

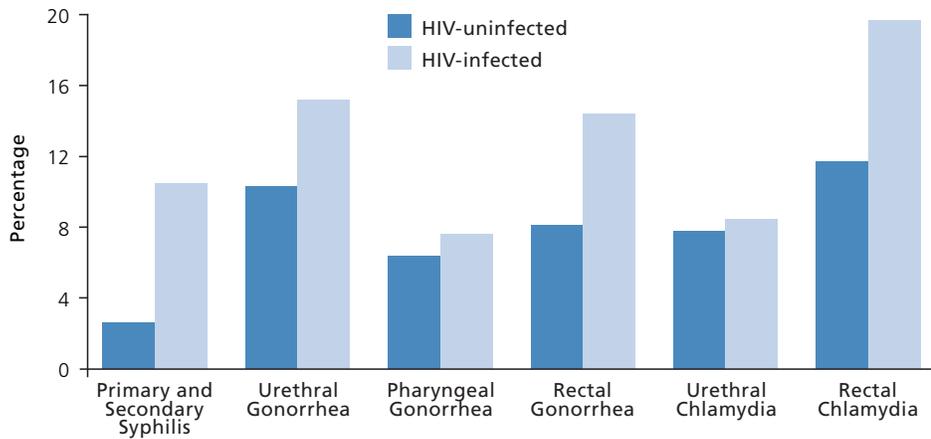


Figure 1. Proportion of men who have sex with men attending sexually transmitted diseases clinics with primary and secondary syphilis, gonorrhea, or chlamydia, classified by HIV serostatus. Adapted from the 2010 Sexually Transmitted Diseases Surveillance Report.¹

Anogenital Ulcerative Lesions

Diagnosing anogenital lesions based only on medical history and physical examination can often be inaccurate. HIV can modify the presentation of a coexisting infection, bacterial superinfection may be present, and more than 1 etiologic agent can be present in a genital or perianal lesion. Herpes simplex virus (HSV) and syphilis infections are the most common infectious causes of anogenital lesions. However, point-of-care methods for accurate diagnosis of genital ulcers due to syphilis and genital herpes are not commercially available. Evaluation of persons with genital or perianal ulceration should include a serologic test for syphilis, HSV culture or PCR testing, and a test for *Haemophilus ducreyi* in settings where chancroid is prevalent. Genital herpes, syphilis, and chancroid have been associated with an increased risk of HIV transmission. Other etiologies of anogenital lesions that are not sexually transmitted include aphthae, drug eruption, yeast, trauma, fixed drug eruption, and psoriasis or lichen planus, which can sometimes ulcerate.

In general, the best management approach is to treat for the diagnosis considered most likely based on clinical presentation and epidemiologic circumstances. For example, if syphilis is suspected, empiric treatment with benzathine penicillin should be administered before serologic test results are available, because early treatment

decreases the possibility of ongoing transmission. Biopsy of genital, anal, or perianal ulcers can help identify the cause of ulcers if there is considerable uncertainty regarding diagnosis or if the ulcers do not respond to initial therapy.

Syphilis

Recent surveillance data from CDC indicate that patients with syphilis, and especially MSM, are more likely to present for care in the secondary stage of disease. MSM have the highest rates of secondary syphilis compared with heterosexual women and men (see Figure 2).¹

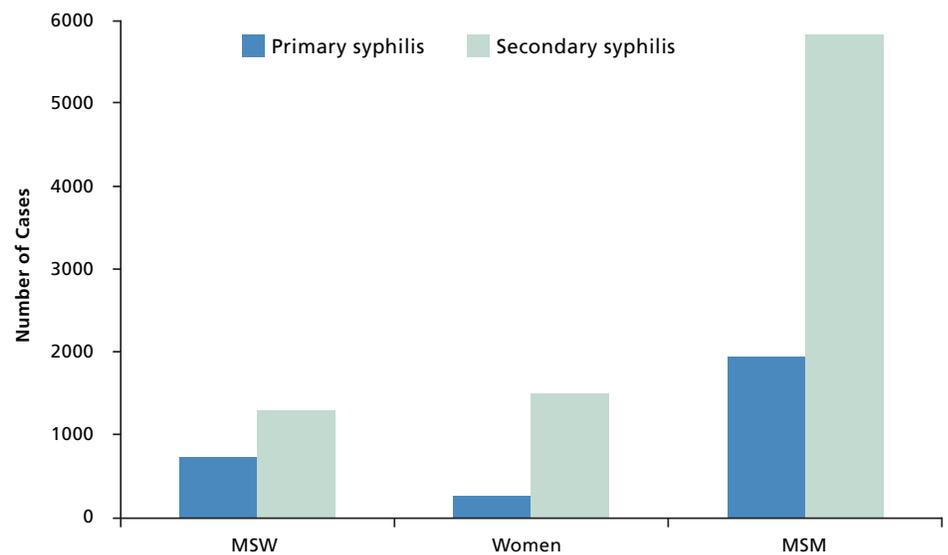


Figure 2. Cases of primary and secondary syphilis among men who have sex exclusively with women (MSW), women, and men who have sex with men (MSM). Adapted from the 2010 Sexually Transmitted Diseases Surveillance Report.¹

Although more rapid progression or severe disease might occur in HIV-infected persons with advanced immunosuppression, the clinical manifestations of syphilis are similar to those in HIV-uninfected persons. The most common clinical manifestations, macular, maculopapular, papulosquamous, or pustular skin lesions, can involve the palms and soles, and may be accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache. However, other characteristics may include numerous deep ulcers, simultaneous manifestation of primary and secondary syphilis, and lues maligna (papulopustular skin lesions that evolve into ulcerative lesions with sharp borders and a dark central crust). Uveitis and meningitis are more common in HIV disease, with neurologic involvement occurring at any stage. Syphilis is a disseminated disease, with invasion of the central nervous system occurring early in infection, irrespective of a patient's HIV serostatus.

Definitive diagnosis of early syphilis requires darkfield microscopy or PCR of lesion exudate or tissue. There are no commercially available tests for direct detection of *Treponema pallidum* (TP). The diagnosis of syphilis is often based on serologic testing for early syphilis, and is usually performed with

a nontreponemal test followed by a treponemal test. However, approximately 30% of nontreponemal tests performed during primary syphilis can report false-negative results, and up to 20% of cases of primary syphilis may present with oral manifestations that are often missed by the patient and the health care practitioner.

Newer technologies include reverse-sequence treponemal screening methods such as enzyme immunoassays (EIAs) and chemiluminescence immunoassays (CIAs). The traditional approach to syphilis diagnosis consists of quantitative rapid plasma reagin (RPR) followed by a *Treponema pallidum* passive particle agglutination (TP-PA) assay or other treponemal test. However, this approach may miss primary infection because of false-negative results in early infection.

In the reverse-sequence approach, EIA or CIA tests are performed, and if positive, are followed by quantitative RPR. This strategy identifies those persons with previous treatment for syphilis and those with untreated syphilis. If the nontreponemal test is negative, a different treponemal test should be performed to confirm the results of the initial test. If a second treponemal test is positive, persons with previous treatment will require no further management unless sexual history suggests reexposure. Those without a history of syphilis treatment should be offered treatment. If a second treponemal test is negative, further evaluation or treatment is not indicated.

This reverse-sequence serologic testing can lead to problems in interpretation and decision-making when nontreponemal and treponemal tests are discordant. In a study conducted in several laboratories in New York City, 56% of 6548 EIA-positive samples were RPR negative.² In a more recent study in several cities, 57% of 4834 EIA- or CIA-positive samples were RPR negative.³ The proportion of false-positive EIAs or CIAs was affected by patient risk level, with false-positive results occurring in 46% of low-risk patients (including pregnant women) and 14% of high-risk patients (eg, MSM).

Unusual serologic responses have been observed among HIV-infected persons with syphilis. The patient shown in Figure 3A had advanced HIV disease with ulcerative nodular syphilis that was not diagnosed for months because of absence of a serologic response to syphilis. This phenomenon may be seen when the concentration of cardiolipin antibody is high, precluding visible agglutination using RPR testing. Dilution of sera 1:100 was required in this instance before agglutination was visible.

The patient shown in Figure 3B had advanced HIV disease with a CD4+ cell count of 3/ μ L and had hypopigmented rash for several months. During this time, extensive evaluation including many nontreponemal and treponemal tests was negative. It was initially thought that the patient had T-cell lymphoma or severe psoriasis. A skin biopsy revealed a lymphocytic infiltrate; treponemes were identified via silver stain of the tissue. Biopsy should be performed in instances in which the diagnosis is uncertain in persons with advanced HIV infection who fail to mount an adequate immune response because of advanced immunosuppression.

The treatment of choice for primary, secondary, and early latent syphilis is 2.4 million units of benzathine penicillin administered by intramuscular (IM) injection. There is no evidence of clinical benefit of additional doses of benzathine penicillin or other additional antibiotics in early syphilis, despite the somewhat common practice of administering 3 weekly doses of benzathine penicillin.

Use of any penicillin alternatives (eg, for patients with penicillin allergy) should be undertaken with close clinical and serologic monitoring. Several retrospective studies support the use of doxycycline for early syphilis; however, many of these studies were conducted in HIV-uninfected persons. Limited studies suggest that ceftriaxone also is effective for early syphilis, but the optimal dose and duration have not been clearly defined.

Azithromycin has not been well-studied in HIV-infected persons with

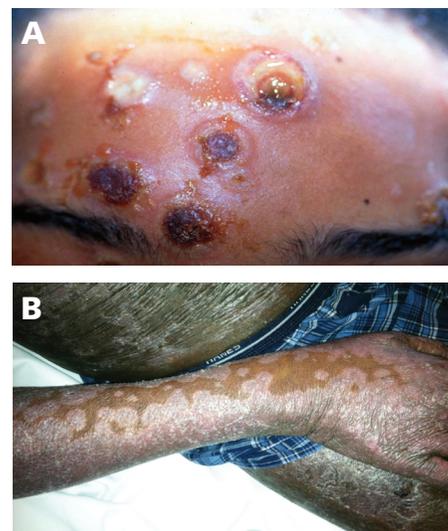


Figure 3. Presentations of syphilis in HIV-infected patients. **A:** Ulcerative nodular syphilis. **B:** Seronegative secondary syphilis.

early syphilis, and azithromycin resistance and treatment failures have been reported, especially in MSM. A recent study in 12 US cities showed that azithromycin resistance is fairly widely distributed and is more common in MSM than in men who have sex exclusively with women.⁴ Azithromycin should not be used in MSM, or in pregnant women because it does not reliably cross the placenta.

HSV Infection

HIV-infected persons can have prolonged, severe, or atypical presentations of genital herpes. External genital lesions may not be evident. Figure 4 shows an HIV-infected woman with vaginal discharge and numerous cervical ulcerations. The classic, ulcerative, external genital lesions may be absent in some instances and should prompt

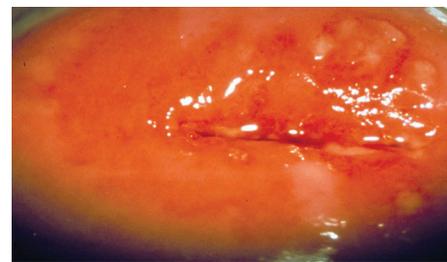


Figure 4. Cervical lesions in an HIV-infected patient with herpes simplex virus-2 infection.

the clinician to consider alternative clinical presentations such as herpetic cervical infection that can present as recurrent vaginal discharge.

Many persons may have also mild or unrecognized infection but can shed virus intermittently in the genital tract. A recent study observed 498 immunocompetent, HSV-2-infected men and women in whom self-administered genital swabbing was performed daily for 30 days. Persons with asymptomatic HSV-2 infection shed virus in the genital tract less frequently than those with symptomatic infection, but the quantity of virus shed during subclinical shedding was comparable to the quantity in those with symptoms.⁵ This suggests that the management of genital herpes should address the chronic nature of the disease, not just the treatment of genital ulceration.

Suppressive therapy with antiviral agents is effective in decreasing the clinical manifestations of genital herpes in HIV-infected persons. Higher doses or a more prolonged duration of acyclovir therapy may be required. Use of daily suppressive therapy can reduce the likelihood of the emergence of drug resistance, as demonstrated in patients with immunosuppression due to bone marrow transplantation.⁶ Resistance to antiviral therapy should be suspected for lesions that persist despite appropriate therapy. Clinical management of acyclovir-resistant HSV includes intravenous foscarnet or topical imiquimod or cidofovir gel.⁷

Nongonococcal Urethritis

Several organisms can cause urethritis. Nongonococcal urethritis is diagnosed when examination indicates urethral inflammation without gram-negative intracellular diplococci. *Chlamydia trachomatis* can be present in 15% to 40% of cases. *Mycoplasma genitalium*, an emerging pathogen, accounts for 15% to 25% of nongonococcal urethritis. Currently, *M genitalium* is very difficult to culture and may be identified with PCR tests available only in the research setting. Consideration of *M genitalium* infection as an etiologic agent of nongonococcal urethri-

tis may be important, as this organism responds more effectively to azithromycin than doxycycline. Other pathogens can include certain *Ureaplasma* strains, *Trichomonas vaginalis*, genital herpes, adenovirus, enteric bacteria, and *Candida* species.

Gonorrhea

Gonorrhea is important because of the high burden of disease, the reproductive and economic consequences of infection, and progressive antibiotic resistance. *Neisseria gonorrhoeae* has demonstrated a remarkable ability to develop resistance to numerous antimicrobials over the last 60 years, including sulfonamides, penicillins, tetracyclines, and fluoroquinolones. Because of concerns about emerging gonococcal antimicrobial resistance, the CDC developed a Gonococcal Isolate Surveillance Project to monitor antimicrobial susceptibility in the United States. The data from this project have provided a rational basis for recommended gonococcal treatment regimens.

The most effective treatment for uncomplicated gonococcal infection of the cervix, urethra, or rectum is combination therapy with ceftriaxone 250 mg IM and either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days. However, declining gonococcal susceptibility and treatment failure to cephalosporins (most notably with oral regimens) is occurring worldwide. The prevalence of isolates in the United States with elevated cefixime minimal inhibitory concentrations has increased substantially in the western United States and in MSM. These patterns are worrisome and may indicate the early development of clinically significant gonococcal resistance to cephalosporins. There have been oral and parenteral cephalosporin treatment failures reported around the world, but this has not yet been seen in the United States.

Providers who identify a gonococcal treatment failure should perform culture and antimicrobial susceptibility testing of relevant clinical specimens.

The practitioner should consult an infectious diseases specialist for treatment advice and report the case to the CDC through the local or state health department within 24 hours. The initial treatment regimen should include ceftriaxone 250 mg IM plus azithromycin 2 g orally. A test of cure should be conducted 1 week after retreatment, and clinicians should ensure that the patient's sexual partners from the preceding 60 days are promptly evaluated and treated.

Gastrointestinal Syndromes

Proctitis is a sexually transmitted gastrointestinal (GI) syndrome associated with anorectal pain, rectal discharge, or tenesmus. Gonorrhea, chlamydia, genital herpes, and syphilis are the most common pathogens involved. Proctocolitis is associated with symptoms of proctitis, diarrhea, or abdominal cramps and may be caused by *Campylobacter*, *Shigella*, *Salmonella*, *Entamoeba histolytica*, or lymphogranuloma venereum serovars of *C trachomatis*. Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis, and it may occur among those persons whose sexual practices include oral-anal contact. *Giardia* is the most frequently implicated pathogen causing enteritis.

Lymphogranuloma venereum (LGV) is an invasive, chlamydial infection that can lead to chronic fistulas and strictures if untreated, and its presentation can resemble inflammatory bowel disease (Crohn's disease). Figure 5 shows the mucosa of an HIV-infected patient with LGV who had an initial diagnosis of inflammatory bowel disease based on clinical presentation and histology of a colonic biopsy. The finding of painful perianal ulcers or mucosal ulcers detected on anoscopy should raise suspicion for LGV in MSM or women who report receptive anal intercourse. Rectal *C trachomatis* infection can be diagnosed using NAAT on rectal specimens.

Commercially available NAATs are not FDA-approved for testing of rectal specimens, but can be used by labora-

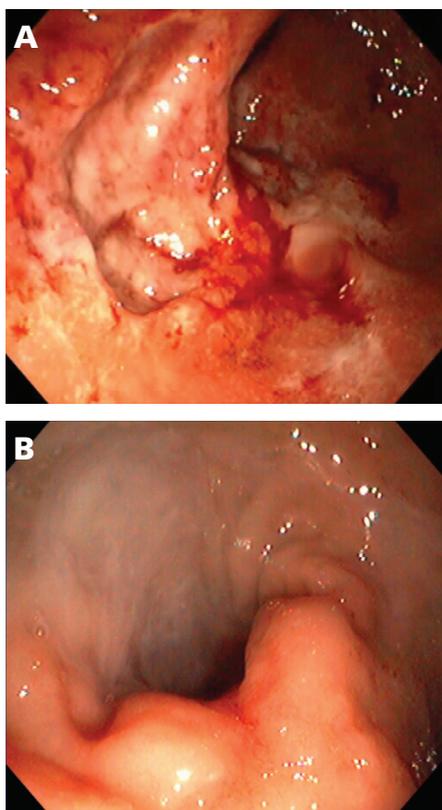


Figure 5. A: HIV-infected man with lymphogranuloma venereum presenting with rectal pain and bleeding for 1 month. Colonoscopy showed friable erythematous, nodular mucosa (15 cm from anus), ulcers, and purulence. Histology showed severe, acute inflammation and ulceration. **B:** Photograph of normal colonic mucosa after treatment.

tories that have met all regulatory requirements for an off-label procedure. Additional molecular testing (genotyping) can then be used to differentiate LGV from non-LGV chlamydial strains.⁸ However, if this infection is suspected in HIV-infected MSM with anorectal chlamydia, treatment with doxycycline 100 mg orally twice daily for 3 weeks should be administered while awaiting genotyping results.

Hepatitis A and B viruses can be sexually transmitted and vaccination is recommended in those without previous infection or vaccination. Sexual transmission of HCV can occur, especially among HIV-infected MSM. HIV-infected MSM can acquire HCV infection after initial serologic screening; therefore, patients with any new or unexplained increase in alanine aminotransferase should

be tested for acute HCV infection. In HIV-infected MSM with high-risk sexual behavior or concomitant ulcerative sexually transmitted infections, routine HCV testing should be considered.

Trichomoniasis

Trichomonas vaginalis (TV) is the most prevalent curable STI in the United States and in the world. Trichomoniasis is frequently diagnosed among women infected with HIV, with prevalences reported between 6.1% and 52.6%,⁹ depending on the testing method used for diagnosis. TV infection in HIV-infected women might enhance HIV transmission by increasing genital shedding of the virus and treatment for TV has been shown to reduce HIV shedding.^{10,11}

For sexually active women who are HIV-seropositive, screening for trichomoniasis is recommended at entry into care, with subsequent screening performed at least annually. TV testing is recommended based on the reported prevalence of infection, the effect of treatment at reducing vaginal HIV shedding, and the potential complications of upper genital tract infections among women who are left untreated.^{12,13} Rescreening 3 months after completion of therapy should be considered among HIV-seropositive women with trichomoniasis, a recommendation based on the high proportion of recurrent or persistent infection and the association between HIV and TV infections.⁷

The standard treatment recommendations for trichomoniasis have been based on studies that were conducted in HIV-seronegative persons. However, a recent randomized clinical trial in HIV-infected women demonstrated that a single 2 g dose of oral metronidazole was not as effective as metronidazole 500 mg twice daily for 7 days for treatment of trichomoniasis.¹⁴ Therefore, a multidose nitroimidazole treatment regimen for trichomoniasis can be considered in HIV-infected women. It is also likely that concomitant bacterial vaginosis influences treatment response.¹⁵

HPV Infection

High-risk human papillomavirus (HPV) subtypes (eg, 16, 18) are associated with cervical, penile, vulvar, vaginal, and anal cancers. HPV is also associated with oropharyngeal cancers, recurrent respiratory papillomatosis, and anogenital warts. There is an increase in the incidence of oral cancers caused by HPV, such that the prevalence of oral cancers in the United States is expected to exceed the prevalence of HPV-associated cervical cancer by 2020.¹⁶ Patients with HPV infection need to be counseled regarding the risk of genital and oral transmission. Updated guidance on HPV, genital warts, and counseling messages is available.¹⁷

Because of the increased incidence of anal cancer in HIV-infected MSM, screening for anal intraepithelial neoplasia by cytology can be considered.¹⁸ However, evidence is limited concerning the natural history of anal intraepithelial neoplasias, the reliability of screening methods, the safety and response to treatments, and the programmatic considerations that would support this screening approach.

Sinecatechins ointment (15%), made from green tea leaves, is a new patient-applied treatment for genital warts. However, the safety and efficacy of this therapy in HIV-infected patients has not been established. It has adverse effects (eg, vitiligo) similar to imiquimod.

The quadrivalent or the bivalent HPV vaccine can be used for women and girls, but the quadrivalent vaccine is the only approved vaccine for men and boys. Cervical cancer screening is recommended regardless of vaccine status. Publication of the updated HIV Opportunistic Infection Prevention and Treatment Guidelines is anticipated in 2012 and recommendations regarding HPV vaccination are likely to be addressed.

Prevention of STIs

Current efforts to prevent STIs should be based on risk assessment, screening, treatment, and partner services. As noted, routine evaluation of HIV-infected persons for STIs is important

because an incident infection is an objective marker of unprotected sexual activity that may result in HIV transmission. Certain STIs can also increase plasma HIV shedding. Other important strategies include high-intensity behavioral counseling and preexposure vaccination (hepatitis A virus, hepatitis B virus, and HPV vaccines). Consistent and correct use of latex condoms by men can reduce the risk of acquiring other STIs (eg, HIV, gonorrhea, chlamydia, trichomoniasis) via mucosal fluids. Agents that disrupt the anal or vaginal epithelium (eg, spermicide with nonoxynol-9) can damage mucosal tissues and provide a portal of entry for sexually transmissible agents. Finally, male circumcision has been shown to reduce the risk for HIV and some STIs in heterosexual men in Africa (eg, high-risk HPV types and genital herpes).

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