

The Clinical Manifestations and Treatment of Sexually Transmitted Diseases in Human Immunodeficiency Virus–Positive Men

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Sexually transmitted diseases (STDs) occur commonly in sexually active human immunodeficiency virus (HIV)–positive men. STDs may have atypical presentations, can cause significant morbidity in persons with HIV infection, and may increase the risk of HIV transmission. Thus, the appropriate diagnosis and treatment of STDs in this population are extremely important. The clinical manifestations and treatment of several common STDs in HIV-positive men are reviewed. Further research is needed to define effective management and screening strategies for STDs in men with HIV infection.

Sexually transmitted diseases (STDs) can present significant diagnostic difficulties when they occur in HIV-positive persons, and the appropriate treatment and follow-up of an HIV-positive patient with an STD occasionally differs from the standard clinical approach to treating HIV-negative patients. Given our current understanding of the role of STDs in increasing the risk of HIV transmission [1–3], appropriate management of STDs in HIV-positive persons is essential. The purpose of this review, therefore, is to describe the clinical presentations of and treatment options for the most common STDs in HIV-positive men: syphilis, herpes, human papillomavirus infection, gonorrhea, *Chlamydia* infection, and nonchlamydial, nongonococcal urethritis. Where relevant, we also present data describing the impact of STDs on HIV shedding and transmission.

SYPHILIS

The Centers for Disease Control and Prevention (CDC) has recently embarked on a national syphilis eradication campaign. Although there have been significant strides in syphilis control nationally [4], outbreaks of syphilis among men who have sex with men (MSM) continue to occur [5, 6]. Almost three-quar-

ters of the cases of early syphilis among MSM in Seattle from 1997 through 1999 occurred in HIV-positive men [5].

Although cross-sectional studies have documented an association between HIV transmission and syphilis [7], data from prospective studies have been less consistent in defining a causal association between syphilis and incident HIV infection. Recent in vitro studies have suggested mechanisms by which syphilis might increase HIV transmissibility: *Treponema pallidum* has been shown to induce HIV-1 gene expression in human monocytes [8] and has been found to promote the expression of the monocyte β -chemokine receptor CCR5 [9], a coreceptor for HIV transmission [10, 11].

Clinical manifestations. Numerous case reports indicate that syphilis can present in highly atypical and aggressive forms in HIV-positive persons; however, the frequency of such atypical presentations is unclear. HIV-positive patients with syphilis may be more likely than HIV-negative persons to present with persistent chancres [12], ulcerative skin lesions [13, 14], gummatous disease [15, 16], and early ocular involvement [17]. In a prospective study that included 101 HIV-positive and 440 HIV-negative patients with syphilis, Rolfs et al. [18] noted that HIV-positive patients were more likely to have multiple chancres and to experience Jarisch-Herxheimer reactions than were HIV-negative patients (22% vs. 12%, respectively; $P = .02$). Although the power of this study was limited, in that only 45% of the target sample size was enrolled, no other substantive differences in clinical presentations were noted.

In the late 1980s, case reports documented accelerated

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courses of neurosyphilis and apparent cases of neurorelapse in patients with HIV infection [19–21]. The prospective study by Rolfs et al. [18] did not support these findings; specifically, accelerated neurological clinical presentations were not noted in HIV-positive patients with early syphilis, nor was the rate of clinically defined treatment failure higher in this group than in HIV-negative persons. The authors did note that pretreatment CSF pleocytosis (defined as >5 WBC/mm³) was significantly more common among HIV-positive patients than among those without HIV infection (43% vs. 22%, respectively; $P < .01$); however, ~30% of HIV-positive patients may have CSF pleocytosis in the absence of neurosyphilis or other CNS infection [22], making the significance of this finding uncertain.

Thus, although concomitant HIV infection clearly broadens the scope of possible clinical presentations in patients with syphilis, the frequency of highly atypical or aggressive forms of syphilis among such patients appears to be lower than was originally thought.

Serology and CSF interpretation. Although the results of serological tests for syphilis are generally accurate for patients with HIV infection, their interpretation should be approached with an understanding of their limitations in this setting. Nontreponemal serological tests for syphilis (serum Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR] tests) in particular appear to have less reliable results for HIV-positive persons than for those without coinfection. A positive result of serum VDRL or RPR tests along with a negative treponemal antibody test—a “biological false-positive” result—has been reported to be more frequent among those infected with HIV than among the general population [23, 24]. However, this association may to a significant extent reflect confounding by injection drug abuse, a known cause of biological false-positive results. Indeed, in a study whose authors stratified MSM into those who did and those who did not abuse injection drugs, the association between biological false-positive results and HIV seropositivity was present only among those who used injection drugs [25]. One group of investigators has reported that false-negative results of nontreponemal tests due to the prozone phenomenon are more common in HIV-positive pregnant women [26].

The results of treponemal tests for syphilis—the treponemal hemagglutination and microhemagglutination assays and the fluorescent treponemal antibody absorption tests—may also be affected by HIV serostatus. Once positive, treponemal assays usually remain positive for life, but several retrospective studies [27, 28] and one prospective study [29] have indicated that HIV-positive patients with treated syphilis appear more likely to serorevert to negative treponemal test results than are HIV-negative patients treated for syphilis.

Evaluation of CSF in patients coinfecting with syphilis and HIV also poses unique problems. The diagnosis of neurosyphilis

is based on abnormalities in ≥ 1 of 3 parameters of the CSF, regardless of the HIV serostatus of the patient: WBC count, VDRL test result, and protein level. As has been noted, however, roughly one-third of HIV-positive persons may have CSF pleocytosis at baseline; an elevated CSF protein level also appears relatively common in those with HIV infection (present in ~20% of patients in one study) [22]. Although a positive result of a CSF VDRL test remains a specific, if not a particularly sensitive, means of diagnosing neurosyphilis, pleocytosis or elevated CSF protein levels must therefore be interpreted carefully in HIV-positive persons. Unfortunately, attempts to develop testing methods that have increased sensitivity and specificity for neurosyphilis have made little progress; the detection of *T. pallidum* in the CSF by use of PCR has thus far proven insensitive and of little clinical utility for HIV-positive patients [18, 30], and CSF “index tests,” such as the treponemal hemagglutination and microhemagglutination assay index and the intrathecal *T. pallidum* assay index, have similarly proven of limited diagnostic value [31].

Treatment for syphilis. The 1998 CDC STD treatment guidelines [32] do not differ in treatment recommendations for early latent syphilis or neurosyphilis in patients with and those without concomitant HIV infection. Because of occasional reports of failure of treatment for syphilis among HIV-positive patients [33], some have questioned the efficacy of standard therapies for syphilis in HIV-positive patients. However, prospective data do not support differential treatment recommendations for those with HIV infection. “Enhanced therapy” for early syphilis (a single dose of 2.4×10^6 U of im benzathine penicillin G, plus 10 days of probenecid 500 mg orally t.i.d. and amoxicillin 2 g orally t.i.d.) did not improve outcomes of HIV-positive patients compared with standard therapy in a carefully designed, prospective study [18]. A recently published prospective study [30] of ceftriaxone (2 g iv once daily for 10 days) suggests that ceftriaxone may prove an effective alternative to iv penicillin in treating HIV-positive patients with secondary syphilis and CNS involvement.

In the absence of proven benefit from alternative therapeutic regimens, the standard of care for treating patients with HIV and syphilis remains as follows: a single dose of 2.4×10^6 U of im benzathine penicillin G for patients with primary, secondary, and early latent syphilis; 3 weekly doses of 2.4×10^6 U of im benzathine penicillin G for patients with late latent syphilis or syphilis of unknown duration; and $18\text{--}24 \times 10^6$ U/day of iv aqueous crystalline penicillin G ($3\text{--}4 \times 10^6$ U q4h) for 10–14 days for patients with neurosyphilis. For those persons with neurosyphilis for whom iv therapy is not feasible and in whom good compliance can be assured, an alternative regimen is 2.4×10^6 U of im procaine penicillin daily plus of 500 mg oral probenecid orally 4 times daily for 10–14 days. Close follow-up of HIV-positive patients to assess for treatment failure and

the development of neurosyphilis is essential (see below). Issues pertaining to the treatment of HIV-positive patients with syphilis have recently been reviewed [31], and the literature from which the 1998 guidelines were drawn has been summarized [34].

Despite the challenge of interpreting CSF abnormalities in patients with HIV infection, lumbar punctures should be performed before syphilis treatment for all HIV-positive patients with late latent syphilis or syphilis of unknown duration. Some experts recommend examination of CSF samples from HIV-positive patients with early syphilis. However, abnormal results of testing of CSF during early syphilis are not very specific predictors of those at risk to develop neurosyphilis, and thus routine lumbar puncture for HIV-positive persons with early syphilis is not recommended in the most recent CDC STD treatment guidelines [32].

Responses to therapy in patients with HIV and syphilis may also prove difficult to interpret. Although some studies have demonstrated a normal decline in titers of serum nontreponemal tests after therapy for syphilis in patients with HIV [29, 35, 36], other studies have shown delayed serological responses in coinfecting patients [18, 24, 37]. In addition, 2 studies have demonstrated that the reversion of CSF abnormalities may be delayed in some HIV-positive patients with neurosyphilis [37, 38], although in these studies, the majority of patients with persistently abnormal CSF parameters showed no evidence of clinical treatment failure. Therefore, the clinical relevance of a delayed serological or CSF response to therapy in patients with HIV who have been treated for syphilis is unclear. However, frequent clinical and serological evaluation of patients with HIV who have been treated for syphilis is clearly prudent; current CDC STD treatment guidelines suggest evaluations at 3, 6, 9, 12, and 24 months after therapy for HIV-positive patients with early syphilis and at 6, 12, 18, and 24 months after therapy for those with latent syphilis or syphilis of unknown duration [32]. Failure to show a 4-fold (2 dilutional) decline in serum nontreponemal test titer at 6–12 months in patients with early syphilis or 12–24 months in patients with late latent syphilis or syphilis of unknown duration should prompt an examination of the CSF. In patients with neurosyphilis and HIV infection, serial lumbar punctures at 6-month intervals should be done after therapy. Strong consideration should be given to administering a second course of treatment for those with neurosyphilis whose CSF cell counts fail to normalize within 18–24 months, especially if such a finding is accompanied by a <4-fold decline in serum or CSF VDRL test titer.

HERPES SIMPLEX VIRUS

Infection with herpes simplex virus type 2 (HSV-2) is among the most prevalent STDs worldwide [39–42]. In the United

States, HSV-2 is the most common cause of genital ulcers [43, 44], and data from the National Health and Nutrition Examination Survey have shown that the seroprevalence of HSV-2 in the United States population is approximately 1 person in 5, which is a 30% increase since the late 1970s [45, 46]. HSV-2 seroprevalence is considerably higher among HIV-positive persons than in the general population [39, 44, 47], and HIV can be detected by PCR in nearly 70% of genital ulcers due to HSV-2 in HIV-positive men [48]. In addition, studies have shown that HSVs stimulate HIV-1 mRNA transcription [49] and viral replication [50, 51]. Despite the significant potential for increased transmissibility of HIV in those with HSV infection, epidemiological data regarding herpes and HIV transmission remain conflicting [52, 53].

Clinical manifestations and HSV shedding. Infections due to HSV among MSM typically present as penile or perianal lesions or as herpetic proctitis. In the majority of cases, these infections are due to HSV-2, although HSV-1 has recently been shown to account for an increasing proportion of initial herpetic infections in MSM [54]. Nongenital manifestations of HSV infection include oral ulcers and herpetic whitlow. Primary HSV infections typically follow an incubation period of 2–4 days and may be accompanied by painful regional lymphadenopathy. Skin lesions due to HSV may present in different stages, including pustules, vesicles, shallow painful ulcers, and crusted lesions. HSV urethritis most often presents as dysuria and clear urethral discharge. Patients with symptomatic herpes proctitis usually describe anorectal pain (especially with bowel movements or receptive anal intercourse) and bloody or purulent anal discharge [55, 56]; there may be accompanying sacral radiculopathy and urinary retention, which help in distinguishing HSV from other causes of proctitis. In the absence of herpetic vesicles, which may be absent or difficult to visualize, the findings on anoscopic examination are nonspecific.

Genital HSV recurrences in persons with advanced HIV infection can be severe, producing disfiguring lesions that may show a slow response to therapy. However, in a prospective study of MSM with and without HIV, Schacker et al. [57] found that the majority of HSV-2 shedding was perianal and subclinical in both men with and men without HIV infection. Interestingly, subclinical shedding was more common than clinically apparent shedding even on the penile shaft, an area easily examined for the presence of visible lesions. In this study, HIV-positive men were somewhat more likely than HIV-negative men to demonstrate anogenital HSV lesions during a 2-month follow-up (46% vs. 31%, respectively), but the median duration of recurrent lesions (6 days) did not differ between HIV-positive and HIV-negative men. In a prospective study of men with more advanced HIV infection, the median duration of lesions was 11 days [58]. Although the frequencies of HSV shedding [57] and HSV ulceration [59, 60] appear to be higher among

HIV-positive men with lower CD4 cell counts, both shedding and ulceration vary considerably among men with similar CD4 cell counts.

Diagnosis and treatment of herpes. To confirm the diagnosis of anogenital herpes, fluorescent antibody staining and culture of swabs or biopsy specimens should be done. The sensitivity of culture in the diagnosis of HSV depends on the stage of the lesion, and lower yields should be expected when culturing specimens from lesions that have already crusted over. To diagnose HSV infection in asymptomatic persons with latent HSV-2 infection, commercially available type-specific serological assays are now available [61]. Although the best use of results of type-specific serological tests in the clinical setting is still unclear [62, 63], it is likely that their use as a screening tool for both patients with and those without HIV infection will be demonstrated.

The 1998 CDC STD treatment guidelines [32] recommend that persons with HIV infection receive the same the acyclovir regimens for primary and recurrent herpes and for different sites of infection: 200 mg of oral acyclovir 5 times a day or, more commonly, 400 mg of oral acyclovir t.i.d. (or 5 mg/kg iv q8h in severe cases). The only placebo-controlled study of herpes proctitis—a study of immunocompetent adults—used 400 mg of oral acyclovir 5 times a day [64], and therefore some practitioners prefer to treat herpes proctitis in all patients with higher dosages of acyclovir (i.e., 2 g/day) than those often used for genital herpes.

Valacyclovir (1 g b.i.d.) and famciclovir (500 mg b.i.d.) provide more convenient dosing than acyclovir and are widely used to treat HSV infections in HIV-positive persons. Although high doses of valacyclovir (i.e., 8 g/day) have been associated with thrombotic microangiopathy in persons with HIV and in patients who have undergone bone marrow transplantation, it is believed that the standard, lower doses of valacyclovir can be used safely in HIV-positive patients [32, 65].

No consensus about the use of long-term suppressive therapy for HSV in HIV-positive persons has yet been established. Famciclovir (500 mg twice daily) has been demonstrated in a cross-over, placebo-controlled trial of HIV-positive men to effectively decrease both the frequency of HSV shedding and recurrent genital lesions [58], and suppressive therapy is clearly warranted for some persons with frequent and/or severe symptomatic recurrences of HSV. The efficacy of suppressive therapy in decreasing the incidence of HSV transmission is currently being studied in HSV-2-serodiscordant HIV-negative couples.

Acyclovir-resistant herpes. Infection with acyclovir-resistant HSV is a well-documented clinical problem in the treatment of a small minority of HIV-positive patients [66, 67] and has also been described in persons with other forms of immunocompromise [68, 69]. The prevalence of acyclovir-resistant herpes in persons with HIV is not known but appears low;

in a recent study of HIV-positive MSM, the prevalence of acyclovir resistance was 1.9%, which is similar to that noted in the general population [57]. Although routine susceptibility testing of HSV isolates from patients with HIV is not warranted, antiviral susceptibilities should be determined if lesions fail to respond to standard therapy.

Acyclovir-resistant herpes among patients with HIV has been caused primarily by thymidine kinase-deficient HSV mutant strains [66, 67, 70], which are also resistant to valacyclovir, famciclovir, and ganciclovir. Although thymidine kinase-deficient mutant strains are capable of causing severe disease in patients with HIV [71], these strains do not appear to have intrinsically increased virulence compared with wild type viruses when studied in vitro and in animal models [70]. Thus, the aggressive clinical presentations of some acyclovir-resistant HSV infections most likely reflect the severe degree of immunodeficiency in the affected hosts rather than HSV-specific factors.

Treatment options for acyclovir-resistant herpes in patients with HIV have been recently reviewed [65]. Therapy with iv foscarnet (40 mg/kg q8h), an agent that does not require viral phosphorylation by thymidine kinase, is generally preferred in cases of confirmed acyclovir-resistant HSV infection.

HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) infection is considered to be the most common sexually transmitted disease in the United States [72, 73] and is often subclinical. More than 70 genotypes of HPV are recognized at present; those most commonly associated with anogenital infections include both HPV types considered low-risk for inducing malignant transformation (types 6 and 11) and high-risk types (types 16, 18, 31, and 35). Among men with HIV, types 16 and 18 account for the majority of HPV infections of the anal canal [74, 75]. HPV infection is more common among HIV-positive MSM than among HIV-negative MSM [74–79], and large studies have consistently demonstrated the prevalence of HPV among HIV-positive MSM to be $\geq 85\%$ [75, 77–79]. In contrast, the prevalence of cervical HPV infection in HIV-positive women ranges from 57% to 70% in cross-sectional studies [80–82]. Among men with HIV infection, HPV prevalence increases with decreasing CD4 cell counts [74, 75], probably in part due to reactivation of latent HPV infection.

HPV is spread between male partners primarily through insertive or receptive anal sex. Other possible routes of transmission include oral sex [83], finger-genital contact [84], and contact with the scrotal surface [73]. Circumcision status does not appear to affect the risk for genital HPV infection [85–87].

Clinical manifestations. Anogenital warts most commonly present as verrucous, papular lesions (condylomata acuminata). Keratotic warts, which have a thickened layer that

more closely resembles common plantar or palmar warts, smooth papular warts (small, skin-colored papules), and flat warts are other well-described variants. In the perianal region, condylomata acuminata may be pedunculated. Warts can occur anywhere in the anogenital area, including on the scrotum and in the urethral meatus, anal canal, or crural folds. Anogenital warts do not usually cause symptoms, although itching, trauma-induced bleeding, and, less commonly, superinfection can occur. Patients with perianal warts may mistakenly diagnose themselves as having hemorrhoids. Some investigators have found that the clinical appearance and distribution of anogenital warts in subjects with HIV infection do not appear to differ substantially from those without HIV [88, 89], whereas others report multiple anatomic sites of anal HPV infection to be more common [90].

Intra-anal manifestations of HPV infection are of particular importance, given the association of HPV with anal dysplasia (see below). Warts in the anal canal are usually acuminate or papular in appearance, occur at or near the dentate line [88, 89], and often demonstrate characteristically dilated surface vessels most easily visualized with a colposcope [88]. Other intra-anal manifestations that have been described are macular white patches and circumferential rings of warts [88]. Clinical appearance cannot reliably distinguish between anal condylomata with and those without intraepithelial neoplasia [88, 91]. The majority of intra-anal HPV infections among HIV-positive MSM are subclinical [74], and high-grade anal dysplasia has been demonstrated in biopsy specimens from completely normal-appearing rectal mucosa in both men with and men without HIV infection [92]. The use of topically applied 3%–5% acetic acid to whiten areas of hypercellularity due to HPV infections has not generally proven to be an especially sensitive nor specific means for detection of HPV lesions in men [88, 93].

Intraoral manifestations of HPV infection include condylomata acuminata, verruca vulgaris (solitary white lesions), squamous papillomas (pedunculated lesions, generally on the soft palate), and focal epithelial hyperplasia or Heck's disease (painless soft papules on the buccal or labial mucosa resembling flat warts) [94]. Oral warts in HIV-infected persons often contain unusual HPV types [94].

HPV-associated dysplasia and malignancy. Data are conflicting as to whether the incidence of anal cancer is increased among HIV-positive men, and the mechanisms underlying the pathogenesis of anal intraepithelial neoplasia (AIN) and anal cancer remain poorly understood. However, reflecting the known relationship between HPV infection, cervical intraepithelial neoplasia, and cervical cancer, it appears that HPV infection with carcinogenic types is the primary factor responsible for the development of AIN, the precursor of anal squamous cell cancer.

In 2 prospective studies of high-grade anal intraepithelial neoplasia that were conducted before the advent of highly active antiretroviral therapy [78, 95], incident high-grade AIN was 2–4 times more common among HIV-positive MSM than among HIV-negative MSM. HIV-positive MSM with lower CD4 cell counts more frequently have high-risk types of HPV in the anal canal, as detected by use of hybrid capture techniques [75], as well as a greater risk of incident high-grade AIN [78, 95]. Smoking, which has been associated with invasive anal cancer [96], has also been linked to the presence of abnormal anal cytology independent of CD4 cell count [97].

Treatment of anogenital warts. The treatment of anogenital warts in patients with HIV can pose difficulties both because of the large number and size of lesions that may be present and because of the high rate of recurrence after treatment. To date, however, few data exist that specifically address the comparative efficacy of treatment modalities for anogenital warts in HIV-positive persons. The 1998 CDC STD treatment guidelines do not specify different treatment approaches for HPV infections in HIV-positive patients, except to recommend that more frequent biopsies of lesions may be advisable, given the potentially increased risk of squamous cell cancer [32].

Several excellent reviews of treatment options for anogenital warts in immunocompetent patients have recently been published [93, 98]. Modalities that are commonly used to treat HPV in HIV-positive persons include both patient-applied therapies (podofilox, imiquimod) and provider-administered treatments (podophyllin resin, tri- and bichloroacetic acid, cryotherapy, electrocautery, scissor/scalpel excision, and curettage). Preliminary clinical experience with topically applied cidofovir for patients with HIV and genital warts has been promising [99, 100] and merits further study. Oral warts in patients with HIV may be difficult to treat, are generally approached with cryotherapy or surgical excision, and show a high rate of recurrence following therapy [101]. Although some clinicians advocate a more aggressive, excision-based approach to HPV therapy in patients with HIV infection [102], it remains to be seen whether this approach results in improved outcomes.

Two recent studies of HIV-positive women with HPV-related cervical intraepithelial neoplasia [103, 104] suggest that highly active antiretroviral therapy (HAART) may induce regression of cervical dysplasia in some HIV-positive women. It remains to be seen whether HAART will lead to regression of anal dysplasia or whether aggressive antiretroviral therapy may paradoxically increase the incidence of anal cancer by prolonging the life span of patients with HIV infection.

Few data exist to show that condoms prevent the transmission of HPV and whether HPV infection increases the rate of transmission of HIV is not known. Patients with HPV infection should nonetheless be counseled that condom use is clearly of benefit in preventing the transmission of other STDs, including

HIV, and may help prevent superinfection of or bleeding from denuded or friable surfaces during treatment for anogenital warts. Smoking cessation counseling should be offered to HIV-positive patients with anal HPV infection who smoke, given that this population may be at particularly increased risk for anal dysplasia and anal cancer.

Screening and treatment for anal dysplasia. Because the natural history of anal dysplasia is incompletely understood, and because the best means of screening for anal intraepithelial neoplasia is not known, practice guidelines for the diagnosis and management of HPV-associated anal dysplasia have not yet been established. Although a recent study has shown that performing anal Pap smears on MSM every 1–2 years would be as cost-effective as screening for cervical cancer, as measured by quality-adjusted life expectancy benefits [105], most experts agree that further research on the natural history and treatment of anal dysplasia is needed before anal Pap smears become part of the general medical care of HIV-positive MSM. The clinical utility of HPV typing also remains unestablished; however, knowledge of HPV types in a given lesion or patient is unlikely to affect treatment decisions at present, and thus routine typing is not currently recommended.

Until the utility of routine screening for anal dysplasia is established, clinicians should have a low threshold both for performing anoscopic examinations of patients with symptoms referable to the anal canal and for performing biopsies of suspect lesions. Appropriate treatment for persons found to have high-grade anal intraepithelial neoplasia remains unclear, but surgical removal [106] or ablation of lesions by cautery or laser [88] have been suggested. Such decisions clearly need to be made on a case-by-case basis; for example, pursuing aggressive therapy for high-grade dysplasia may be most appropriate for those patients with a reasonable life expectancy [107]. Unless symptoms are present, men found to have low-grade anal neoplasia should be followed closely but not treated.

GONORRHEA

Although gonorrhea remains prevalent among MSM, relatively little has been published in recent years about the epidemiology or clinical presentations of gonorrhea in MSM or in subjects with HIV. Gonorrhea can be transmitted by insertive or receptive anal intercourse and, less efficiently, by fellatio [108]. Recent evidence, including a well-documented outbreak of gonorrhea among young MSM in Australia [109]; coincident increases in the cases of rectal gonorrhea, hepatitis B virus infection, and HIV infection among MSM in England and Wales [110]; and recently described increases in unprotected anal intercourse and rectal gonorrhea in San Francisco [111], underscores the fact that anogenital gonorrhea remains an important marker of high-risk sexual behavior among MSM.

Epidemiological data are conflicting as to whether gonorrhea plays a role in increasing the transmissibility of HIV-1. Some studies have shown an association with increased acquisition of HIV infection [112–114], whereas others have found no significant association [115, 116]. Substantive data do, however, link gonorrhea to increased HIV shedding in semen: Cohen et al. [117] demonstrated an 8-fold increase in seminal HIV-1 RNA shedding in men with gonococcal urethritis, and found that levels of HIV-1 in semen decreased after effective gonococcal therapy. Similar results have been described by use of seminal HIV-1 DNA as a marker of HIV shedding [118]. The effect of rectal gonorrhea on the rectal shedding of HIV is not known but is currently under study.

Clinical manifestations. The clinical presentation of urethral gonorrhea is familiar to most clinicians and is typified by the onset of dysuria and mucopurulent urethral discharge after an incubation period of up to 1 week. In a review of some 1700 cases of gonorrhea among MSM, Sherrard and Barlow [119] suggest that the clinical manifestations of gonorrhea in men may be changing: the combination of discharge and dysuria occurred in only 55% of men with gonococcal urethritis, although discharge alone remained a relatively sensitive diagnostic symptom, occurring in 82% of infected men.

Anorectal gonorrhea was once thought to be universally asymptomatic. In fact, symptoms may occur in ~20% of patients [119] and can include mucopurulent anorectal discharge, rectal bleeding, pruritus ani, pain, tenesmus, and constipation. In men with rectal gonorrhea, the mucosa may appear friable, purulent, and erythematous on anoscopic examination or can appear completely normal [56, 120]. Most pharyngeal gonococcal infections are asymptomatic [108, 119], although pharyngitis and cervical lymphadenitis are occasionally reported. Disseminated gonococcal infections have been noted sporadically in patients with HIV [121], but no data exist to suggest that this or other complications of gonorrhea are more common in subjects with HIV infection.

Diagnosis and treatment of gonorrhea. The diagnosis of urethral gonorrhea can be made in up to 95% of men on the basis of the results of a Gram stain of urethral secretions. The sensitivity and specificity of ligase chain reaction and PCR testing of urine samples for gonorrhea are >98% compared with standard culture techniques. In general, Gram stains of rectal specimens are an insensitive means for diagnosing rectal gonorrhea as compared with culture [119, 122], although the use of anoscopy to collect rectal secretions may increase the sensitivity of Gram stain considerably [123]. Amplification methods and DNA probe assays have not yet been studied in sufficient detail to warrant their routine use in the diagnosis of anorectal or pharyngeal gonococcal infection, and thus culture remains the primary means for diagnosis in these cases.

Treatment recommendations for urethral, pharyngeal, and

rectal gonorrhea do not differ for HIV-positive persons [32]. Cefixime (a single oral dose of 400 mg), ceftriaxone (a single im dose of 125 mg), ciprofloxacin (a single oral dose of 500 mg), and ofloxacin (a single oral dose of 400 mg) are all highly efficacious for treatment of uncomplicated gonococcal urethritis and proctitis due to sensitive strains of *Neisseria gonorrhoeae* (GC); gonococcal pharyngitis, although generally more difficult to eradicate, can be treated with the same doses of antibiotics with reasonable efficacy (>90%). Recent reports of increasing fluoroquinolone resistance in GC isolates internationally [123a, 123b] and in Hawaii [123c] have raised concerns about the use of fluoroquinolones for empiric treatment of gonorrhea in certain settings, and the CDC's forthcoming 2001 STD treatment guidelines will therefore recommend that fluoroquinolones not be used as therapy for GC acquired in Hawaii or in Southeast Asia. Whichever the drug chosen, therapy for gonorrhea should always include therapy for concomitant chlamydial infection (see next section). Screening of sex partners of MSM with gonococcal infection is especially important, given the frequency with which anorectal and pharyngeal infections are asymptomatic.

CHLAMYDIA AND OTHER AGENTS OF NONGONOCOCCAL URETHRITIS

Nongonococcal urethritis (NGU) encompasses urethral infections caused by *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium*. Rarely, HSVs cause NGU. *C. trachomatis* is the most commonly identified cause of NGU, accounting for 15%–40% of cases. Although evidence suggests that the proportion of cases of NGU caused by *C. trachomatis* may be decreasing [124, 125], chlamydial infection remains a common cause of urethritis among men [126–128], and it is a significant cause of both urethritis and proctitis among MSM [55, 56, 120].

Evidence regarding genital HIV shedding in men with NGU or chlamydial urethritis is limited. Although seminal shedding of HIV-1 has been found by some investigators to be increased in men with asymptomatic NGU [129] and symptomatic chlamydial urethritis [130], others have not found increased seminal HIV-1 shedding in men with NGU [117]. Prospective data from cohorts of high-risk HIV-negative women suggest that chlamydial infection may be a risk factor for HIV-1 acquisition [114, 116].

T. vaginalis is a less commonly identified cause of NGU in men than is *C. trachomatis* [124, 125], although data are limited, because men are not routinely tested for infection with *Trichomonas*. Recent research from Africa, however, suggests that *T. vaginalis* may be a more common cause of symptomatic and asymptomatic urethritis in men than has been appreciated and may account for 15%–20% of cases of urethritis in certain

populations [131, 132]. In addition, trichomonal urethritis has been associated with significantly elevated concentrations of HIV-1 in seminal plasma [132]. In light of the potential implications of these and other data, and in the context of a recently developed and highly sensitive culture system for *T. vaginalis* [133], some authors have called for a reevaluation of the place of trichomonal infection in the current diagnostic and management algorithms for NGU [134, 135].

U. urealyticum is identified relatively frequently in studies of men with symptomatic urethritis when care is taken to culture for the organism [125, 127, 136]. Further research is needed to firmly establish and better characterize its role as a pathogen in urethritis, because it is also found commonly in asymptomatic men. Several studies indicate that *M. genitalium*, a related organism, may be a significant cause of nonchlamydial NGU [137–139]; indeed, *M. genitalium* was implicated as the sole infecting organism in 14% of men with NGU in a recent study [140]. Interestingly, the prevalence of asymptomatic urethral carriage of both *U. urealyticum* and *M. genitalium* has been shown to be several-fold higher in men with AIDS than in either HIV-positive men without AIDS or HIV-negative control patients [141]. The effects of either organism on HIV transmission and HIV shedding, if any, remain undefined.

Clinical manifestations. The incubation period for chlamydial urethritis has been difficult to establish because asymptomatic infection is common [142, 143]. Urethral discharge in chlamydial urethritis is, in general, less copious and purulent than the discharge typical of gonococcal infection; however, there is considerable overlap between the clinical presentations of gonococcal and nongonococcal urethritis. Clinical features cannot reliably distinguish between the urethritis caused by *T. vaginalis*, *U. urealyticum*, *M. genitalium*, or *C. trachomatis*. We are aware of no published data on variations in the clinical manifestations of these infections in HIV-positive men.

Proctitis and proctocolitis due to *C. trachomatis* are often asymptomatic, especially when they are caused by non-lymphogranuloma venereum (LGV) serovars. Both symptomatic anal ulceration [56] and symptomatic proctitis [56, 120] appear more common in patients infected with LGV serovars (L1, L2, or L3), which are found primarily in Africa, South America, Southeast Asia, and the Caribbean. Symptoms of proctitis, when present, include mucopurulent or bloody rectal discharge, tenesmus, and anorectal pain; LGV serovars more commonly produce fistulas as well as inguinal and deep iliac adenopathy [56]. Strictures may occur as a late complication of chlamydial proctitis. The findings of anoscopy for patients with chlamydial proctitis are nonspecific and include a friable rectal mucosa, ulcerations, and discharge [56, 120].

Diagnosis and treatment of NGU. The diagnosis of NGU, identification of the causal agent, and recommended treatments do not differ for men with and men without HIV infection.

The workup and treatment of NGU in immunocompetent men have been recently reviewed [124]. Both doxycycline (100 mg orally twice daily for 7 days) and azithromycin (a single oral dose of 1 g) have cure rates of >85% for the treatment of NGU. However, ~10% of *Ureaplasma* strains have been noted to be tetracycline resistant and another 10% have been noted to be erythromycin resistant (simultaneous resistance to both antibiotics is rare) [144], and failure rates are higher with azithromycin or doxycycline therapy in nonchlamydial NGU [124, 125]. Trichomonal infection requires the administration of metronidazole (a single oral dose of 2 g) for cure.

Persistent or recurrent urethritis after treatment for NGU may be due to reinfection with *Chlamydia* or another organism, untreated trichomonal urethritis, or failure of the original treatment to clear *Ureaplasma* infection. Clinicians should be aware that the results of ligase chain reaction and PCR tests for *C. trachomatis* may remain positive for up to 3 weeks after the completion of effective therapy for *Chlamydia*, presumably because of excretion of dead organisms. Partner referral for evaluation and treatment is an essential component of the management of any patient with urethritis.

The diagnosis of chlamydial proctitis is made by means of culture or immunofluorescent staining of rectal swabs or biopsy specimens; unfortunately, PCR and ligase chain reaction have not yet been studied sufficiently to recommend their use in the diagnosis of proctitis. The treatment for chlamydial proctitis caused by non-LGV serovars is usually 7–14 days of doxycycline (100 mg orally twice daily) [56, 120]. The treatment of LGV strains is usually a course of therapy with doxycycline for 21 days.

RECOMMENDATIONS FOR STD SCREENING IN HIV-POSITIVE MSM

Although both the Infectious Diseases Society of America and the CDC are currently considering recommendations for STD screening in HIV-positive men, no specific guidelines currently exist for STD screening of men with HIV infection. Our recommendations are presented here only as a rough guide for clinicians and should be tailored to economic and logistic constraints as well as to local STD prevalence.

Given the recent increases in the incidence of early syphilis, gonorrhea, and *Chlamydia* infection among MSM in some US cities, annual STD screening appears reasonable for sexually active HIV-positive men in most settings. For asymptomatic men who report engaging in receptive anal sex, rectal specimens should be cultured for gonococci and *C. trachomatis*, whereas for those who report engaging in insertive anal sex, urethral specimens should be cultured for *C. trachomatis*, or DNA amplification tests for *C. trachomatis* should be performed on first-void urine specimens. Urethral gonococcal cultures or urine

gonococcal DNA amplification tests should also be performed for men who have urethral discharge on examination or have a positive leukocyte esterase test result, as determined by a urine dipstick test. For men who have engaged in receptive fellatio, cultures for pharyngeal gonococci should be performed, regardless of the presence or absence of symptoms. Serological screening for syphilis is recommended during the baseline evaluation of patients with HIV infection and should be done at least once a year thereafter for patients living in cities with a high incidence of syphilis. For HIV-positive men with CD4 cell counts <200 cells/mm³, the results of type-specific HSV serology studies may help to predict those at greatest risk for recurrences and may be help to decide whether to use suppressive or episodic antiviral treatment. Studies are underway to assess the utility of HSV serological screening for HIV-positive persons. The utility of regular anal Pap smears for HIV-positive MSM remains controversial; until such time as guidelines are developed, the evaluation of MSM with symptoms referable to the anal canal should include an assessment for HPV-related dysplasia by anoscopy or colposcopy and subsequent biopsy of suspect lesions.

Although STD screening is an important aspect of the care of HIV-positive persons, effective counseling is also crucial. The importance of general STD education and of emphasizing the need to use of condoms cannot be overstated, especially in light of evidence that suggests a relaxing of attitudes toward safe sex practices by some HIV-positive men in the era of potent antiretroviral activity [145, 146]. Risk assessment of MSM should include questions about high-risk sexual behaviors, such as sex-associated drug use, participation in high-risk sexual practices (i.e., “barebacking”), and attending venues for the purposes of anonymous sex (e.g., bath houses, sex clubs, and parks) [147]. It may be helpful to counsel HIV-positive men that HIV can be readily detected in the semen [148], rectal secretions [149], and pharynx [150] of HIV-positive men who have undetectable plasma HIV-1 loads. Finally, we have found it useful to emphasize to men that unprotected oral sex is not necessarily “safe” in regards to the transmission of HIV and other STDs [151].

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