Management of Herpes Simplex Virus Type 2 Infection in HIV Type 1–Infected Persons

Lara B. Strick, Anna Wald, and Connie Celum

Departments of Medicine, Division of Allergy and Infectious Diseases, Epidemiology, and Laboratory Medicine, University of Washington, Seattle

Human immunodeficiency virus type 1 (HIV-1)–infected persons have high rates of herpes simplex virus type 2 (HSV-2) infection, ranging from 50% to 90% in studies of HIV-infected populations from different parts of the world. Genital herpes in persons with HIV type 1 (HIV-1) infection is associated with more-severe and chronic lesions, as well as increased rates of asymptomatic genital shedding of HSV-2. Nucleoside analogues (acyclovir, valacyclovir, and famciclovir) decrease the frequency and severity of HSV-2 recurrences and asymptomatic HSV-2 reactivation and are effective, safe, well-tolerated drugs in patients with HIV-1 infection. These anti-HSV drugs may result in additional clinical and public health benefits for persons with HIV-1 and HSV-2 coinfection by decreasing HIV-1 levels in the blood and genital tract. Given these benefits, HIV–1–infected persons should be routinely tested for HSV-2 infection using type-specific serologic tests. Persons with HSV-2 infection should be offered HSV-2 education and treatment options. Studies to quantify the potential clinical and public health benefits of treating individuals who have HIV-1 and HSV-2 coinfection with anti-HSV therapy are underway.

Herpes simplex virus type 2 (HSV-2) is a highly prevalent sexually transmitted infection [1–3]. With the advent of better diagnostic assays (e.g., PCR) in conjunction with dramatic decreases in chancroid and syphilis, genital herpes is recognized as the most common cause of genital ulcer disease in both the developed and developing world [4–8]. HSV-2 infection is also one of the most common infections among HIV-infected persons, partly because of the shared route of sexual transmission [3, 9–13]. HSV-2 affects 50%–90% of HIV–1–infected patients, with the highest infection rates among heterosexuals in sub-Saharan Africa and men who have sex with men in the Americas [3, 14–19].

Anogenital herpes was one of the first opportunistic infections described in persons with AIDS, and persistent herpetic ulceration is an AIDS-defining illness [20, 21]. Despite the early recognition of genital herpes as an opportunistic infection, there has been a lack of emphasis on the clinical management of HSV-2 coinfection in HIV–1–infected persons and no clear guidelines exist for diagnosis and therapy. This review focuses on issues related to clinical manifestations, natural history, diagnosis, and treatment of HSV-2 coinfection in HIV–1–infected adults.

ASYMPTOMATIC HSV REACTIVATION

Similar to immunocompetent persons, most HIV-infected persons with HSV-2 infection are asymptomatic [22, 23]. However, almost all HSV–2–seropositive persons shed HSV-2 genitally, regardless of prior reported genital lesions [22–24]. Prospective studies show that persons coinfected with HIV-1 and HSV-2 experience more frequent episodes of mucosal shedding of HSV-2 than do HIV-uninfected persons, most of which are subclinical [23–25] (table 1). The degree of immunosuppression is an important factor in determining the HSV–2 reactivation rate, with a correlation between the mucosal rate of HSV–2 shedding and plasma HIV–1 RNA level and an inverse correlation with CD4+ cell counts [15, 23–26] (table 1). However, HSV-2 is frequently shed even in persons with CD4+ cell counts >400 cells/mm³, with substantial variability observed between persons at all CD4+ cell counts [24, 25].

Shedding of HSV–2 is not only more frequent but also higher in quantity among HIV–infected persons with lower CD4+ cell counts [25]. In addition, HSV–2 reactivations in HIV–infected men are more often at multiple anatomic sites, compared with reactivations in HIV–uninfected men [23, 27, 28]. The higher frequency and multiple anatomic sites of mucocutaneous shedding of HSV–2 and the higher HSV–2 DNA copy number in
Table 1. Genital shedding of herpes simplex virus type 2 (HSV-2) in HIV-infected persons.

<table>
<thead>
<tr>
<th>Study, patient group by CD4+ cell count</th>
<th>Date</th>
<th>Population, location</th>
<th>Method of HSV-2 detection</th>
<th>No. of samples</th>
<th>Frequency of symptomatic HSV-2 infection, %</th>
<th>Frequency of HSV-2 detection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augenbraun et al. [24]</td>
<td>1995</td>
<td>HIV-infected women, United States</td>
<td>Culture</td>
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<td>...</td>
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<tr>
<td>All patients</td>
<td>...</td>
<td>...</td>
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<td>106</td>
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<tr>
<td>≤200 cells/mm³</td>
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<td>...</td>
<td>...</td>
<td>79</td>
<td>...</td>
<td>10</td>
</tr>
<tr>
<td>Wright et al. [26]</td>
<td>2003</td>
<td>HIV-infected women, United States</td>
<td>Culture</td>
<td>...</td>
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</tr>
<tr>
<td>All patients</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>242a</td>
<td>89b</td>
<td>33</td>
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<tr>
<td>Schacker et al. [23]</td>
<td>1998</td>
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<td>Culture</td>
<td>4167</td>
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<td>10</td>
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<tr>
<td>Corey et al. [25]</td>
<td>2004</td>
<td>HIV-infected MSM, United States</td>
<td>PCR</td>
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<td>...</td>
</tr>
<tr>
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<td>9797</td>
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<td>...</td>
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<td>...</td>
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</tr>
<tr>
<td>Mostad et al. [15]</td>
<td>2000</td>
<td>HIV-infected women, Kenya</td>
<td>PCR</td>
<td>...</td>
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<td>...</td>
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<tr>
<td>All patients</td>
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<td>...</td>
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<td>272</td>
<td>35c</td>
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<td>&gt;200 cells/mm³</td>
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<td>...</td>
<td>224</td>
<td>...</td>
<td>16</td>
</tr>
</tbody>
</table>

NOTE. MSM, men who have sex with men.

a Patients were receiving anti-HSV-2 therapy during 41 of the visits.

b At visits when HSV-2 was detected, clinically apparent lesions were present 71% of the time; other symptoms, such as perineal pain or pruritis, were noted at an additional 18% of the visits.

c Includes only genital ulceration as a symptom.

HIV-1–infected persons, especially those at lower CD4+ cell counts, likely increases the probability of HSV-2 transmission to sexual partners [23, 24].

SYMPTOMATIC GENITAL HERPES

Among HIV-infected persons with symptomatic HSV-2 infection, the clinical presentation of genital herpes varies. HSV-2 infection can be unrecognized in HIV-1–infected persons, because lesions are small or confined to the perianal region and are therefore difficult for patients to see. On the other end of the spectrum, HIV-infected persons can also have more frequent or persistent anogenital herpetic lesions, which may become extensive, deeply ulcerated, and necrotic, primarily in patients with low CD4+ cell counts [8, 29] (figure 1). Mucocutaneous manifestations of HSV-2 infection may have an atypical location or appearance, leading to delays in diagnosis and in initiation of appropriate therapy [24, 30–32]. The differential diagnosis of HSV-2 lesions includes other ulcerative sexually transmitted infections, such as syphilis and chancroid, staphylococcal and other bacterial infections, pyoderma gangrenosum, squamous cell carcinoma, and Behcet’s disease. More serious and systemic HSV manifestations include esophagitis, dissemination, meningoencephalitis, hepatitis, pneumonitis, and retinal necrosis, all of which are relatively rare, even in patients with advanced HIV infection [32–41].

DIAGNOSIS OF HSV-2 INFECTION

Clinical diagnosis of genital HSV-2 infection in HIV-infected persons is unreliable, and both false-negative and false-positive diagnoses occur [42]. HSV PCR of genital lesions has 2- to 4-fold higher sensitivity than viral culture in determining the etiologic diagnosis of genital ulcer disease [43, 44]. For testing of persons without a clinical history of genital herpes, gG-based type-specific serological testing that can accurately diagnose and distinguish HSV-1 from HSV-2 with high sensitivity and specificity (>95%) should be used [45–47]. These assays appear to have similar performance characteristics for HIV-infected persons.

We recommend offering serological HSV-2 testing routinely to HIV-infected persons as part of their initial evaluation to identify asymptomatic or unrecognized HSV-2 infection [48]. The inclusion of routine HSV-2 testing in recent screening guidelines for HIV-infected persons is mentioned as an option; we think the recommendations need to be strengthened [49–
Patients identified as being coinfected with HSV-2 and HIV-1 should be appropriately counseled and offered anti-HSV suppressive therapy to reduce symptomatic and subclinical HSV-2 reactivation. Concerns about psychosocial distress in persons who are seropositive for HSV-2 have been diminished by studies showing that the effect is limited and transient [54–56]. Pending the outcome of studies that are underway, the use of suppressive acyclovir to decrease HIV-1 transmission or improve the clinical course of the HIV-1 infection may become additional important reasons for early diagnosis of HSV-2 infection in HIV-infected persons. HSV-1 has been reported to be an increasingly more common cause of primary genital herpes, particularly among men who have sex with men [57] and young persons [58–60]. However, genital HSV-1 reactivates much less frequently than genital HSV-2 [61–63]; although it is still possible that HSV-1 (oral or genital) has interactions with HIV that are similar to those for HSV-2, such data are lacking at this time. Thus, the focus of efforts to diagnose genital herpes in HIV-infected persons should rely on HSV-2–specific serological tests.

HSV INFECTION TREATMENT OPTIONS

Antiviral treatment of HSV infection with nucleoside analogues (acyclovir, valacyclovir, and famciclovir) has been the mainstay of therapy for genital herpes, with 2 decades of experience with acyclovir, which is now available in generic formulations. These antivirals inhibit the replication of HSV-1, HSV-2, and varicella-zoster virus selectively, because phosphorylation requires a virally encoded thymidine kinase. They have a high therapeutic index and are safe, well-tolerated, and effective in HIV-infected patients. The early observations of thrombotic microangiopathy associated with large doses of valacyclovir (8 g per day) used for the prevention of cytomegalovirus disease in HIV-infected patients has not been observed with the lower doses of valacyclovir that are used for treatment of HSV infection [64]. The most common adverse events among patients receiving valacyclovir were nausea and headache, with rates that were not statistically different from those for the placebo arm. Neutropenia or other myelosuppressive effects noted with use of ganciclovir have not been associated with use of acyclovir, famciclovir, or valacyclovir. Importantly, these antivirals do not have any significant interactions with antiretroviral medications used for treatment of HIV-1 infection.

Suppressive therapy. Because symptomatic HSV-2 infection can be more severe and asymptomatic shedding can be more frequent in HIV-1–infected persons, long-term anti-HSV suppressive therapy should be considered. Several studies have shown that acyclovir, valacyclovir, and famciclovir effectively suppress HSV-2 reactivation in persons coinfected with HIV-1 and HSV-2 (table 2) [27, 65, 66]. Breakthrough reactivation in patients receiving suppressive therapy is infrequent, short, and often asymptomatic [27]. If repeated breakthrough recurrences do occur during suppressive HSV-2 therapy, the suppressive dosage of acyclovir can be increased to 800 mg administered 2 or 3 times per day or higher until a clinical response is achieved, or the bioequivalent dosage increase if using valacyclovir or famciclovir [67, 68]. If there is a lack of clinical response despite a higher dosage, susceptibility testing should be considered to assess for possible acyclovir resistance.

Episodic therapy. Symptomatic outbreaks of genital herpes tend to respond more slowly to anti-HSV therapy in HIV-infected patients, especially patients with lower CD4+ cell counts, and higher doses of anti-herpes medications may be required for resolution of symptoms. Typically, symptomatic herpes lesions in an HIV-infected person respond to episodic therapy in 5–14 days, whereas HIV-uninfected adults will usually have complete resolution in 5–7 days.
HSV RESISTANCE TO ANTIVIRALS

The emergence of acyclovir-resistant HSV strains was first documented soon after acyclovir was introduced [72]. Acyclovir resistance has been described in persons with and without prior antiviral exposure [73–75]. Usually, the mechanism is a deficiency of HSV thymidine kinase or, less commonly, enzymatic alterations in thymidine kinase or DNA polymerase [76, 77]. Isolation of drug-resistant HSV from immunocompetent persons has remained infrequent (<1% of isolates) [78–81]. Surveillance studies indicate that acyclovir resistance is somewhat more common, but rates of acyclovir resistance are still <5% among HIV-infected persons [26, 80, 82, 83]. Despite more frequent and prolonged use of acyclovir, the prevalence of acyclovir-resistant strains has remained stable over the past 20 years among both immunocompetent and immunosuppressed persons [75, 79, 83–87]. Drug-resistant HSV-2 isolates have been demonstrated to have reduced fitness in animal models, which may explain the lack of documented transmission in humans and the low prevalence of drug-resistant HSV-2 strains [88].

The emergence of occasional drug-resistant strains probably occurs in every host, but it often is transient and reflects local mucosal variants [89, 90]. At times, acyclovir-resistant HSV presents a clinically important problem for HIV-1–infected persons. Health care providers need to recognize, however, that the detection of drug-resistant virus in vitro is not always clinically relevant, because many infections still respond well to standard therapy. Therefore, HSV resistance testing should only be ordered for patients who have experienced clinical failure, rather than as part of routine surveillance of HIV-1–infected persons [89]. The plaque reduction assay using viral isolates is the most commonly used test of antiviral susceptibility, because results most closely correlate with clinical response [89]. Although certain mutations in HSV-2 have been identified in association with acyclovir resistance, genotypic testing is not currently available for clinical use [91–96].

If there is a poor response to therapy, and the isolate is found to be resistant to acyclovir, intravenous foscarnet is indicated, because all acyclovir-resistant strains are resistant to valacyclovir and most are also resistant to famciclovir [97]. Although foscarnet is the drug of choice for the treatment of drug-resistant HSV infection, several topical alternatives offer limited efficacy when treatment is constrained by renal toxicity. Cidofovir gel (1%) and foscarnet cream (1%), when applied to herpetic lesions, have been shown to promote healing, cessation of viral shedding, and pain relief for patients with acyclovir-resistant HSV infection [98, 99]. Even if a person has had previous laboratory-documented drug-resistant HSV infection, once the episode has resolved, usually the acyclovir-sensitive wild-type virus reactivates [83, 89]. However, case reports of recurrent acyclovir-resistant HSV infection, perhaps caused by mucosal persistence of the virus, have been reported among severely immunocompromised persons [100–103].

OTHER TREATMENT CONSIDERATIONS

The effect of HSV-2 infection on the natural history of HIV-1 infection. HSV-2 reactivation appears to increase plasma HIV-1 levels, which might adversely affect the natural history of HIV-1 infection [104, 105]. Recent analyses of persons with HIV-1 infection from Rakai, Uganda, have indicated that HSV-2 infection was associated with an ~0.5 log$_{10}$ copies/mL higher serum HIV-1 level both soon after seroconversion and during established chronic HIV-1 infection [106]. These data corroborate findings from Mole et al. [107], who reported that a clinical herpetic outbreak among men coinfected with HIV-1 and HSV-2 increased plasma HIV RNA levels [105]. Thus, frequent HSV reactivation may lead to increased plasma HIV-1 levels, thereby adversely affecting survival.

The survival advantage seen in persons with HIV-1 infection who received long-term administration of high-dose acyclovir...
provides further evidence that HSV-2 infection influences the natural history of HIV-1 infection, even though some of the trials were not originally designed to assess this effect [108–110]. A meta-analysis of 8 randomized trials involving 1792 participants and 2947 person-years of follow-up indicated that acyclovir (administered at a dosage of ≥3200 mg per day) offered a significant survival benefit for HIV-1–infected persons (hazard ratio, 0.78; 95% CI, 0.65–0.93) [111]. In a more recent study of 126 persons seropositive for HSV-2 and HIV-1, the protective benefit of acyclovir on the rate of progression of HIV-1 disease to AIDS was minimal when HAART was included in the model [112]. The mechanism by which acyclovir prolongs survival is unclear, but most likely the effect is mediated via suppression of HSV-2, thereby interfering with HIV-1 upregulation during HSV-2 reactivations. Several in vitro studies demonstrated that HSV-2 gene products (e.g., ICP-0, ICP-4, ICP-27, Us11) and cytokines upregulate HIV-1 in coinfected cells, in part through transactivation of HIV-1 long terminal repeats [113–116].

To expand on these epidemiologic and biologic observations, proof-of-concept trials are assessing the prospective effect of HSV-2 suppression on plasma and genital HIV-1 levels. Among 12 men coinfected with HIV-1 and HSV-2, Schacker et al. [104] noted a reduction in HIV-1 plasma load of 35% or 0.3 log_{10} copies of HIV-1 RNA (P = .032) after adjusting for CD4+ cell count during HSV suppression with acyclovir. Most recently, Nagot et al. [117] observed that the mean HIV-1 RNA load in plasma was 0.5 log_{10} copies/mL lower among 140 women coinfected with HIV-1 and HSV-2 in Burkina Faso during valacyclovir suppression than it was among patients in the placebo arm. These studies demonstrate that the use of antiviral medication for HSV suppression is likely to significantly negate the adverse effect that HSV-2 reactivation has on plasma HIV-1 levels, thereby potentially conveying a survival advantage.

The effect of HSV-2 infection on HIV-1 transmission. HSV-2 may be fueling the HIV-1 epidemic by increasing HIV acquisition and transmission, particularly in Africa, where HSV-2 and HIV prevalence rates are the highest in the world. Observational data indicate that genital ulcer disease, the majority of which is due to HSV-2 infection, increases the probability of HIV-1 transmission by ~4-fold on a per-contact basis among monogamous HIV-1–discordant heterosexual couples from Rakai, Uganda, after controlling for serum HIV-1 RNA level in the index partner [118]. Although HSV-1 infection is increasingly common as a cause of primary genital herpes in the developed world [57–60], its interactions with HIV-1 shedding and infectiousness have not been well characterized.

Most prospective studies of HIV-1 infectiousness have focused on surrogate measures, such as HIV-1 RNA levels in anogenital secretions or from genital lesions, because of the inherent difficulty in studying sexual transmission among couples [15, 23, 24, 117, 119]. HIV-1 can be readily isolated from genital herpetic ulcers in coinfected persons, sometimes with higher viral loads than are found in plasma, demonstrating biologic plausibility for the epidemiologic observations that HSV-2 increases risk of sexual HIV-1 transmission [7, 120–123].

Recent data suggest that HSV-2 may also be an important factor in the vertical transmission of HIV-1. Mothers who transmitted HIV-1 to their infants were found to be more likely to have genital herpes recurrences at term, to be HSV-2 seropositive, and—among those mothers experiencing HSV-2 reactivation in the third trimester—to have higher HIV-1 plasma loads [124–126].

Thus, the benefits of suppressive anti-HSV therapy in an HIV-infected person may go beyond clinical benefits for the symptomatic person. HSV-2 treatment can reduce HIV-1 shedding in genital herpes lesions within the first 4–5 days of therapy [119, 120]. In the Burkina Faso placebo-controlled trial, cervicovaginal HIV-1 levels were a mean of 0.35 log_{10} copies/mL lower among women coinfected with HIV-1 and HSV-2 receiving valacyclovir suppression [117]. Current, ongoing, large randomized trials of episodic and suppressive HSV-2 therapy will determine the magnitude of reduction in plasma and mucosal HIV-1 shedding during treatment for HSV-2 infection.
direct assessment of the effect of HSV-2 suppression on HIV transmission is underway in a proof-of-concept trial among HIV-discordant couples, in which the HIV-1–infected partner is also HSV-2 seropositive and is not receiving antiretroviral therapy. Treatment for HSV-2 infection could offer a clinical and public health intervention, especially for HIV-infected persons with intermediate and advanced HIV-1 disease in resource-poor areas who are currently not offered antiretrovirals. Ideally, there will be a prophylactic vaccination for HSV-2 infection, but to date, the candidate HSV-2 vaccines have either no or low efficacy [127–130].

HSV IN THE ERA OF HAART

Few studies have explored the effect of HAART on the clinical course of HSV-2 infection. Although HAART decreases the frequency of symptomatic herpetic lesions, a study did not find that it significantly reduced the rate of genital HSV shedding [131]. Specifically, persons receiving HAART had significantly fewer days with HSV lesions, compared with persons not receiving HAART (percentage of days with HSV lesions, 2.8% vs. 11.3%; P = .001), whereas mucosal HSV-2 shedding was similar (percentage of days positive for HSV DNA, 18% vs. 29%; P = .08) [131]. Thus, when managing the cases of patients who are coinfected with HIV-1 and HSV-2, providers should remember that HAART alone may not reduce the rates of asymptomatic mucosal HSV-2 shedding and, therefore, may not reduce potential infectiousness.

Severe genital HSV-2 lesions have been reported in patients after HAART initiation as an unusual manifestation of immune reconstitution (figure 2) with a delayed response to antiviral therapy, despite documented acyclovir sensitivity [132]. Even when it is not clinically evident, HAART may be associated with an initial period of increased asymptomatic genital HSV shedding [133]. Typically, the severity and frequency of HSV outbreaks improve as the immune system is restored after HAART initiation, but patients with HSV-2 infection can present with severe manifestations even after their CD4+ cell count increases to >500 cells/mm³ [134].

Although HAART has been shown to significantly decrease genital HIV-1 levels and possibly HIV-1 infectiousness, some persons with an undetectable plasma HIV-1 viral load still shed HIV-1 genetically [135–141]. It is unknown whether acyclovir has an additional effect beyond HAART on genital shedding of HIV-1, further reducing the probability of HIV-1 and HSV-2 transmission. In summary, more data are needed to determine the effect of HSV-2 suppression on plasma and genital HIV-1 levels without HAART therapy, as well as during HAART initiation and stable HAART therapy.

CONCLUSION

HSV-2 infection is one of the most common coinfections among HIV-1–infected persons globally, and yet it remains almost universally undiagnosed and untreated. Given the substantial clinical and epidemiologic data about HSV-2 and HIV-1 interactions, providers should test HIV-infected patients for HSV-2 antibody (table 3), which costs $10–$20 with current ELISAs, because HSV-2 frequently reactivates, even when it is clinically “silent” or mild.

On the basis of available data, we recommend that HIV-infected patients with HSV-2 coinfection receive counseling about genital herpes and be offered suppressive acyclovir therapy. The cost of generic acyclovir suppressive therapy can be as low as $45 per year for a dosage of 400 mg administered twice daily. Although episodic treatment of symptomatic genital herpes to reduce the duration and severity of the episode is less costly, it is also likely to be less effective than daily suppressive therapy in preventing HSV-2 (and, potentially, HIV-1) transmission and in improving survival, because most HSV-2 reactivation is subclinical. Given the high seroprevalence of HSV-2 among HIV-infected persons, long-term treatment

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**Table 3. Key points regarding herpes simplex virus type 2 (HSV-2) coinfection in HIV-infected persons.**

| Most persons with HIV-1 infection are also infected with HSV-2. |
| Most HIV-infected persons with HSV-2 coinfection are asymptomatic. |
| Persons coinfected with HIV-1 and HSV-2 have more frequent asymptomatic and symptomatic genital viral shedding, compared with persons with HSV-2 infection alone. |
| The clinical presentation of genital HSV-2 infection in patients with HIV-1 coinfection ranges from extensive, deeply ulcerated, necrotic and chronic lesions to small, unrecognized mucosal or epithelial fissures or ulcers. |

HIV-infected persons should be routinely offered type-specific serologic testing for HSV-2 as part of initial evaluation. HSV-2 reactivation increases HIV-1 levels in plasma, which might adversely affect the natural history of HIV-1 infection. In observational studies, HSV-2 infection has been associated with increased risk of HIV acquisition and transmission. HAART alone does not reduce the rate of asymptomatic mucosal HSV-2 shedding and, therefore, potential infectivity for HSV-2. HSV-2 suppression with antiviral drugs has been demonstrated to reduce both plasma and genital HIV-1 levels in persons coinfected with HIV and HSV-2 and, therefore, may have public health benefits. Despite increasing use of suppressive acyclovir therapy, there has not been an increase in the detection of acyclovir-resistant HSV-2 isolates.
of HSV-2 infection could also have substantial public health benefits.

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