

## GENITAL HERPES SIMPLEX VIRUS (HSV)

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### I. INTRODUCTION

Herpes simplex virus (HSV) is the etiologic agent of genital herpes. Infection with either of the two identified serotypes, HSV-1 or HSV-2, is lifelong. Most genital herpes is caused by HSV-2, whereas most orolabial herpes is caused by HSV-1. However, each serotype can cause disease in either location, and genital HSV-1 may often be acquired through contact with a partner's mouth.<sup>1</sup> Perinatal transmission can also occur, particularly when the mother experiences a primary infection during pregnancy.\*

Serologic studies have documented HSV seropositivity in the overwhelming majority of HIV-infected patients (>95% in some series).<sup>2,3</sup> Orolabial and anogenital disease caused by HSV in HIV-infected patients may vary from that in the non-HIV-infected populations in severity of initial infection or severity or frequency of recurrence. Another difference is that acyclovir resistance is rarely encountered in a non-HIV-infected host, but its frequency is increased in the HIV-infected population. Nevertheless, recommendations for treatment and prophylaxis are similar for the two patient groups.

### II. PRESENTATION

The typical clinical course of genital herpes consists of small papules progressing to painful grouped 1- to 3-mm vesicles on an erythematous base that progress into shallow ulcerations. On mucosal surfaces, vesicles quickly rupture leaving moist erosions or superficial ulcers. Lesions are occasionally limited to small linear erosions or "slits." In approximately 50% of patients, tingling, itching, or paraesthesia may precede primary or recurrent lesions by 24 to 48 hours. Of note, initial infection and reactivations may also be asymptomatic or minimally symptomatic despite active shedding of virus.

Most clinical episodes of genital herpes are recurrent disease. In primary HSV infection, lesions may be numerous, systemic symptoms may be present, and healing typically occurs over 2 to 3 weeks. In recurrent HSV, fewer lesions may appear, less or no systemic symptoms may be present, and healing usually occurs within 10 days. One study found that HSV recurrences in HIV-infected patients increased as CD4 counts decreased to <100 cells/mm<sup>3</sup>.<sup>4</sup>

Most genital herpes in HIV-infected patients present similarly to those in non-HIV-infected patients, although, as listed below, unusual presentations have been described in HIV-infected patients.

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\* For treatment of genital herpes in pregnant HIV-infected women, see *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission*.

### **Clinical Features of Genital Herpes in HIV-Infected Patients**<sup>5,6</sup>

- Lesions may appear as ulcers, “cracks,” or linear fissures
- Lesions may be larger and/or more numerous and may heal slowly
- Lesions may be coinfecting with other pathogens
- HSV is a common cause of proctitis in HIV-infected men who have sex with men (30% in some series)
- HSV lesions in the sacral area may be misdiagnosed as sacral decubiti
- Lesions caused by resistant virus may be especially atypical, more severe, larger, and slower to heal

#### *In patients with low CD4 counts:*

- Giant ulcers have been described (up to 20 cm in diameter)
- Atypical verrucous lesions resembling condyloma have been reported
- Although rare, HIV-infected persons with CD4 counts  $<100$  cells/mm<sup>3</sup> may develop disseminated infection characterized by scattered, discrete, eroded, or crusted erythematous papules or papulovesicles
- Chronic herpetic lesions lasting  $>1$  month are a CDC AIDS-defining illness

### **III. DIAGNOSIS**

#### **RECOMMENDATIONS:**

**Clinicians should diagnose typical genital herpes through the presence of consistent clinical findings upon examination. Diagnosis of chronic nonhealing ulcerated herpes simplex or atypical lesions should be confirmed by culture or either histologic or pathologic examination. Recurrences do not require laboratory confirmation.**

**Clinicians should exclude coinfection with another pathogen, such as syphilis, when a recurring lesion is atypical.**

Diagnostic methods for genital herpes in HIV-infected patients are the same as those for non-HIV-infected patients. Diagnosis of typical genital herpes is usually made through clinical examination. Confirmation of diagnosis through detection of HSV may be useful but is not necessary, and recurrences do not require laboratory confirmation. However, definitive diagnosis may be indicated in cases of unclear etiology and/or cases of suspected syphilis infection. The sensitivity of culture decreases with the duration of the lesion (i.e., less sensitive as lesion heals). HSV antigen detection tests are available, and PCR is available in some specialized laboratories.

Type-specific serologic assays measuring antibody to HSV-specific glycoprotein will reliably identify whether a patient has antibody, and therefore lifelong infection, to HSV-1 and/or HSV-2. Serologic tests do *not* determine whether a given lesion is due to HSV but may be useful for initial episodes. Serologic testing is of limited utility in HIV-infected patients because most series show that the overwhelming majority of HIV-infected patients have antibody to HSV-1 and -2.

## IV. TREATMENT

### RECOMMENDATIONS:

**Acyclovir, valacyclovir, or famciclovir should be used to treat HSV. Specific dosing recommendations and caveats are listed in Table 1.**

**Clinicians should consider the possibility of antiviral resistance if herpetic lesions fail to heal with standard antiviral therapy. Nonadherence and poor absorption should also be considered. The clinician should refer the patient to an HIV or Infectious Disease Specialist when acyclovir-resistant HSV is suspected.**

In general, treatment is oral, well-tolerated, and effective. Systemic antiviral therapy has been shown to improve clinical symptoms and shorten the duration of symptoms and signs; however, treatment does not eliminate the virus. Topical antiviral therapy for genital herpes has minimal efficacy. Intravenous therapy is necessary for severe mucocutaneous progressive disease, visceral involvement (e.g., esophageal or hepatic), or antiviral resistance.

Persistent or recurrent lesions in patients receiving antiviral therapy should prompt an evaluation for poor absorption of the antiviral medication, nonadherence to the regimen, or the development of antiviral resistance.

### Acyclovir-Resistant HSV

#### RECOMMENDATION:

**Clinicians should obtain HSV drug-susceptibility tests, if available, when patients receiving antiviral treatment have persistent or recurrent HSV lesions.**

Most resistant viral isolates are thymidine kinase (TK) deficient and are therefore resistant to acyclovir, valacyclovir, famciclovir, penciclovir, and ganciclovir. If available, drug susceptibility testing should be obtained when patients receiving antiviral treatment have persistent or recurrent HSV lesions.

Treatment options for resistant HSV are listed in Table 1. Following resolution of an episode of acyclovir-resistant HSV, recurrent outbreaks often demonstrate adequate susceptibility to medications used to treat acyclovir-resistant HSV (see Table 1).

**TABLE 1  
TREATMENT OF GENITAL HSV IN HIV-INFECTED PATIENTS<sup>a</sup>**

<b>Stage</b>	<b>Drug Regimen</b>	<b>Comments</b>
<b>Primary outbreak with uncomplicated presentation</b>	<ul style="list-style-type: none"> <li>• Acyclovir 400 mg PO tid<sup>b</sup></li> <li align="center"><i>or</i></li> <li>• Famciclovir 250 mg PO tid or 500 mg bid</li> <li align="center"><i>or</i></li> <li>• Valacyclovir 1g PO bid</li> </ul>	Treatment at onset of symptoms (within 1 day of lesion onset) may abort development of lesions. Treat for 5-10 days based on response.
<b>Recurrences</b>	<ul style="list-style-type: none"> <li>• Acyclovir 400 mg PO tid or 800 mg bid</li> <li align="center"><i>or</i></li> <li>• Famciclovir 250 mg PO tid or 500 mg PO bid</li> <li align="center"><i>or</i></li> <li>• Valacyclovir 500 mg to 1 g PO bid</li> </ul>	
<b>Chronic suppression</b>	<ul style="list-style-type: none"> <li>• Acyclovir 400-800 mg PO bid or tid</li> <li align="center"><i>or</i></li> <li>• Famciclovir 500 mg PO qd or bid</li> <li align="center"><i>or</i></li> <li>• Valacyclovir 1 g PO qd<sup>c</sup></li> </ul>	Consider initiating suppressive therapy (rather than episodic therapy) if symptomatic episodes recur more than 3 times per year. Many can be successfully suppressed with once daily famciclovir or valacyclovir.
<b>Acyclovir-resistant HSV</b>	<ul style="list-style-type: none"> <li>• Foscarnet 40 mg/kg IV q8h for at least 2-3 weeks or until healing</li> <li align="center"><i>or</i></li> <li>• Cidofovir gel 1% applied qd for 5-10 days or until healing<sup>d</sup></li> <li align="center"><i>or</i></li> <li>• Topical trifluridine 1% ophthalmic solution tid until healing<sup>e</sup></li> <li align="center"><i>or</i></li> <li>• Cidofovir 5 mg/kg IV q 2 weeks (limited experience)</li> <li align="center"><i>or</i></li> <li>• Imiquimod 5% cream tid for at least 1 week (limited experience)<sup>f</sup></li> </ul>	Failure of standard therapy should suggest resistance. TK deficiency testing of isolates is not routinely available. Combination therapy may be required in some cases. Foscarnet toxicity includes renal insufficiency and electrolyte abnormalities.

<sup>a</sup> If treating pregnant HIV-infected women, only acyclovir can be used. For more information, see *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission*.

<sup>b</sup> An alternative regimen, acyclovir 200 mg PO 5× per day, may have suboptimal adherence and is therefore not recommended.

<sup>c</sup> Alternative doses are often used (e.g., 500 mg to 1 g PO qd or bid).

<sup>d</sup> Not commercially available and must be compounded by a pharmacist.

<sup>e</sup> Trifluridine solution (Viroptic 1%) is applied after cleansing with H<sub>2</sub>O<sub>2</sub> and then covered with bacitracin and polymyxin ointment and nonabsorbable gauze.

<sup>f</sup> Case reports of HIV-infected patients have demonstrated efficacious results.<sup>7,8</sup>

## V. REACTIVATION AND CHRONIC SUPPRESSIVE THERAPY

Soon after resolution of primary symptoms, HSV becomes latent in the patient's cranial nerve or dorsal root sensory ganglia. In most cases, genital herpes establishes latency in the sacral plexus. Unlike HIV, HSV assumes both a clinical and cellular latency because the virus is believed to replicate at a lower rate during this period. The immune response seems to play an important role in driving HSV into its initial latent state and in maintaining HSV latency.<sup>9</sup> The chronic immunodeficiency brought about by HIV places patients at increased risk for HSV reactivation. HSV replication is believed to be stimulated by a number of factors, including fever (thus the term fever blister), sun exposure, concurrent viral infection, and possibly localized trauma, hormonal changes, or stress.<sup>10</sup>

Subclinical reactivation, or viral shedding (detection of virus on mucosal surface without clinical signs/symptoms), of HSV infection is common in HIV-infected and non-HIV-infected patients. HSV-2 reactivation is more frequent in HIV-infected patients.<sup>11</sup> HAART has little impact on subclinical HSV reactivation.<sup>12</sup> Chronic suppressive therapy may be warranted for patients with frequent symptomatic recurrences. Suppressive antiviral therapy has been shown to decrease the frequency of recurrences, to decrease but not eliminate HSV shedding, and to decrease transmission of HSV to non-HSV-infected partners in immunocompetent hosts.<sup>13,14</sup> There is evidence that HSV reactivation is associated with increased HIV RNA levels<sup>15</sup> and that chronic daily HSV antiviral therapy decreases HIV RNA levels to baseline in patients not receiving HAART.<sup>15,16</sup> This has led some authorities to suggest that HSV suppressive therapy be considered in HIV-infected patients who are not receiving effective ARV therapy.<sup>17</sup> Discontinuation of chronic HSV suppression may be indicated when patients have achieved sustained immunologic response from HAART and have not experienced recent HSV reactivation.

## VI. PREVENTION OF TRANSMISSION

### RECOMMENDATION:

**Clinicians should educate HIV/HSV coinfecting patients with genital herpes about the following:**

- **the use of latex condoms to decrease the risk of transmission, including the risk of superinfection if the partner has one or both viruses**
- **the significance of the role of genital HSV infection in potentiating the spread of HIV even in the absence of clinically apparent ulcers and during chronic suppressive therapy**
- **the frequency of potentially infectious viral HSV reactivation even in the absence of clinically apparent ulcers**
- **viral HSV shedding and infectivity are decreased but not eradicated with chronic suppressive therapy**

## **A. Prevention of HIV Transmission**

An increasing number of studies are addressing the role of HSV in promoting local HIV replication and potentiating HIV transmission. Genital ulcers from HSV,<sup>18,19</sup> as well as from syphilis and chancroid,<sup>19</sup> increase the likelihood that genital secretions will contain an infectious amount of HIV. This increases the potential for contact between HIV in genital secretions and genital mucosal cells receptive to HIV infection.<sup>19</sup> As such, clinicians should stress the importance of using effective barrier methods to HIV/HSV coinfecting patients.

### **Key Point:**

The risk of HIV transmission by patients coinfecting with genital ulcer disease is increased by 2 to 6 times because of increased levels of HIV virus in semen and vaginal secretions.<sup>20-22</sup> Conversely, genital ulcers in non-HIV-infected patients disrupt the genital tract lining or skin, which creates a direct entry for HIV.

## **B. Prevention of HSV Transmission**

Viral HSV shedding has been shown to be higher in HIV coinfecting patients than in those who are seropositive for HSV alone,<sup>23,24</sup> indicating the increased risk of HSV transmission by HIV/HSV coinfecting patients. Latex condoms have demonstrated efficacy in reducing transmission of genital HSV infection, and clinically effective chronic suppressive therapy decreases, but does not eliminate, viral HSV shedding and infectivity. The combination of both methods may help further reduce the risk of HSV transmission.

## **VII. MANAGEMENT OF PARTNERS**

### **RECOMMENDATION:**

**Clinicians should consider both the HIV exposure and the STI exposure to partners when HIV-infected patients present with a new STI. Clinicians should also assess for the presence of other STIs.**

### **A. Management of HIV Exposure in Partners**

#### **RECOMMENDATIONS:**

**When HIV-infected patients present with a new STI, clinicians should encourage their partner(s) to undergo HIV testing at baseline, 1, 3, and 6 months. In New York State, HIV diagnoses must be confirmed by a Western blot assay.**

**Clinicians should educate patients to be vigilant for any post-exposure acute HIV symptoms in their partners, such as febrile illness accompanied by rash, lymphadenopathy, myalgias, and/or sore throat. If the partner presents with signs or symptoms of acute HIV seroconversion, a quantitative RNA PCR should be obtained, and consultation with an HIV Specialist should be sought. Positive RNA tests should be confirmed with HIV antibody testing performed within 6 weeks of the RNA test (see [Antiretroviral Therapy: Acute HIV Infection](#), for more information about diagnosis and management of acute infection).**

**Clinicians should offer assistance with partner notification if needed, or refer patient to other sources for partner notification assistance (CNAP, PNAP).**

Presentation of a new STI in HIV-infected patients suggests exposure of HIV to their partners. In this case, offering HIV nPEP to partners is usually not an option because the period prior to STI symptom onset is usually longer than the 36-hour window for initiating HIV nPEP. Therefore, sequential HIV testing of partners for early identification of potential HIV acquisition should be performed. However, if a patient with an HIV exposure does present within 36 hours, evaluation for nPEP should occur (see [HIV Prophylaxis Following Non-Occupational Exposure Including Sexual Assault](#)).

## **B. Management of HSV Exposure**

### **RECOMMENDATIONS:**

**Clinicians should counsel patients to inform all sex partners of their HSV exposure and should educate HSV-infected patients about the risk of transmission to their sex partner(s), including the risk of superinfection if both partners are infected with HSV or HIV.**

**Sex partners who are symptomatic for genital herpes should be treated or referred for treatment.**

HSV-infected patients and, when possible, their sex partners should receive counseling about informing all sex partners of their HSV exposure. Education of sex partners of HSV-infected patients and treatment or referral for treatment of partners who are symptomatic for HSV can further reduce the risk of transmission.

## REFERENCES

1. Lafferty WE, Downey L, Celum C, et al. Herpes simplex virus type 1 as a cause of genital herpes: Impact on surveillance and prevention. *J Infect Dis* 2000;181:1454-1457. [[Abstract](#)]
2. Stamm W, Handsfield H, Rompalo A, et al. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA* 1988;260:1429-1433. [[Abstract](#)]
3. Holmberg SD, Stewart JA, Gerber AR, et al. Prior HSV type 2 infection as a risk factor for human immunodeficiency virus infection. *JAMA* 1988;259:1048-1051. [[Abstract](#)]
4. Bagdades E, Pillay D, Squires S, et al. Relationship between herpes simplex virus ulceration and CD4+ cell counts in patients with HIV infection. *AIDS* 1992;6:1317-1320. [[Abstract](#)]
5. Stewart JA, Reef SE, Pellett PE, et al. Herpesvirus infections in persons infected with human immunodeficiency virus. *J Infect Dis* 1995;21(Suppl 1):S114-S120. [[Abstract](#)]
6. Tong P, Mutasim D. Herpes simplex virus infection masquerading as condyloma acuminata in a patient with HIV disease. *Br J Dermatol* 1996;134:797-800. [[Abstract](#)]
7. Gilbert J, Drehs MM, Weinberg JM. Topical imiquimod for acyclovir-unresponsive herpes simplex virus 2 infection. *Arch Dermatol* 2001;137:1015-1017. [[Abstract](#)]
8. Martinez V, Molina J-M, Scieux C. Topical imiquimod for recurrent acyclovir-resistant HSV infection. *Am J Med* 2006;119:e9-e11. [[Abstract](#)]
9. McGrath BJ, Newman CL. Genital herpes infection in patients with the acquired immunodeficiency syndrome. *Pharmacotherapy* 1994;14:529-542. [[Abstract](#)]
10. Erlich K, Safrin S, Mills J. Herpes simplex virus. In: Cohen PT, Sande MA, Volberding PA, eds. *The AIDS Knowledge Base: A Textbook on HIV Disease*, 2nd ed. New York: Little Brown; 1995:1-6, 12-19.
11. Schacker T, Zeh J, Hu HL, et al. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis* 1998;178:1616-1622. [[Abstract](#)]
12. Posavad CM, Wald A, Kuntz S, et al. Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. *J Infect Dis* 2004;190:693-696. [[Abstract](#)]
13. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004;350:11-20. [[Abstract](#)]
14. DeJesus E, Wald A, Warren T, et al. Valacyclovir International HSV Study Group. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. *J Infect Dis* 2003;188:1009-1016. [[Abstract](#)]
15. Schacker T, Zeh J, Hu H. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis* 2002;186:1718-1725. [[Abstract](#)]
16. Nagot N, Ouédraogo A, Foulongne V, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007;356:790-799. [[Abstract](#)]
17. Corey L, Wald A, Celum C, et al. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: Two overlapping epidemics. *J Acquir Immune Defic Syndr* 2004;35:435-445. [[Abstract](#)]

18. LeGoff J, Weiss HA, Gresenguet G, et al. Cervicovaginal HIV-1 and herpes simplex virus type 2 shedding during genital ulcer disease episodes. *AIDS* 2007;21:1569-1578. [[Abstract](#)]
19. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep* 2002;(RR-6):1-78. [[Abstract](#)]
20. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: The contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;73:3-17. [[Abstract](#)]
21. Dickerson MC, Johnston BA, Delea TE, et al. The causal role for genital ulcer disease as a risk factor for transmission human immunodeficiency virus. *Sex Transm Dis* 1996;429-440. [[Abstract](#)]
22. Telzak EE, Chaisson MA, Bevier PJ, et al. HIV-1 seroconversion in patients with and without genital ulcer disease. *Ann Intern Med* 1993;119:1181-1186. [[Abstract](#)]
23. Mbopi-Keou FX, Gresenguet G, Mayaud P, et al. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. *J Infect Dis* 2000;182:1090-1096. [[Abstract](#)]
24. McClelland RS, Wang CC, Overbaugh J, et al. Association between cervical shedding of herpes simplex virus and HIV-1. *AIDS* 2002;16:2425-2430. [[Abstract](#)]

#### **FURTHER READING**

Centers for Disease Control and Prevention. 2006 Sexually Transmitted Diseases Treatment Guidelines. *MMWR Recomm Rep* 2006;55(RR-11):1-94. Available at: <http://www.cdc.gov/std/treatment/2006/clinical.htm>