

Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common. Among persons aged 14 to 49 years in the United States, the HSV-1 seroprevalence is 47.8%, and the HSV-2 seroprevalence is 11.9%.¹ While most cases of recurrent genital herpes are due to HSV-2, over the past decade, HSV-1 has become an increasing cause of first-episode genital herpes, causing up to 70% of infections in some populations, such as young adult women and men who have sex with men.² Approximately 70% of persons with HIV are HSV-2 seropositive, and 95% are seropositive for either HSV-1 or HSV-2.³ HSV-2 infection increases the risk of HIV acquisition two- to three-fold,^{4,5} and in coinfecting patients, HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions.⁶

Clinical Manifestations

Oral herpes (commonly known as cold sores or fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations of oral HSV-1 include a sensory prodrome in the affected area, rapidly followed by lesions on lips and oral mucosa that evolve in stages from papule to vesicle, ulcer, and crust. The course of illness in untreated patients is 5 days to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is typically caused by HSV-2 and is the most common manifestation of HSV-2 infection. Increasingly, first-episode genital herpes is caused by HSV-1 and is indistinguishable from HSV-2 infection, although recurrences and viral shedding occur less often with genital HSV-1 infection. Typical genital mucosal or skin lesions evolve through stages of papule, vesicle, ulcer, and crust. Ulcerative lesions are usually the only stage observed on mucosal surfaces, but vesicles are commonly seen on skin on or around the genitals (e.g., the penile shaft, mon pubis, thighs). Local symptoms might include a sensory prodrome consisting of pain and pruritus. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.⁷ These classic manifestations occur in some patients, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized. Regardless of the clinical severity of infection, viral shedding on mucosal surfaces occurs frequently and can result in transmission. HSV shedding occurs more frequently in persons with CD4 T lymphocyte (CD4) cell counts <200 cells/mm³ than in those with higher CD4 counts.^{8,9} An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but recurrences and viral shedding occur less often with genital HSV-1 infection.

HSV is a significant cause of proctitis in men with HIV infection who have sex with men and may not be associated with external anal ulcers.¹⁰ In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations can occur. These lesions have been reported most often in those with CD4 counts <100 cells/mm³ and also may be associated with acyclovir-resistant HSV.¹¹ In addition, atypical presentations such as hypertrophic genital HSV,^{12,13} which mimics neoplasia and requires biopsy for diagnosis, may be seen in persons with HIV infection.

The manifestations of non-mucosal HSV infections (e.g., HSV keratitis, HSV encephalitis, HSV hepatitis, herpetic whitlow) are similar to those observed in HIV-seronegative individuals. Disseminated HSV infection is rare, even in profoundly immunosuppressed patients. HSV retinitis manifests as acute retinal necrosis, which can lead rapidly to loss of vision.

Diagnosis

Because mucosal HSV infections cannot be diagnosed accurately by clinical examination, a laboratory diagnosis of all suspected HSV mucosal infections should be pursued.¹⁴ HSV DNA polymerase chain

reaction (PCR), and viral culture are preferred methods for diagnosis of mucocutaneous lesions potentially caused by HSV. PCR is the most sensitive method of diagnosis. HSV detected in genital lesions should be typed as HSV-1 or HSV-2. The frequency of recurrences is greater for HSV-2 than for HSV-1, and therefore knowledge of viral type is helpful for counseling purposes.

Type-specific serologic assays are commercially available and can be used for diagnosis of HSV-2 infection in asymptomatic individuals or those with atypical lesions. Type-specific serologic screening for HSV-2 for persons with HIV infection can be considered. However, providers should be aware that there are some important limitations of currently available serologic tests. In particular, false positive HSV-2 serologic test results occur with the enzyme immunoassay antibody tests, particularly at low index values (1.1–3.5).¹⁵⁻¹⁷ In such situations, confirmatory testing with a second serologic test is recommended in the 2015 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease Treatment Guidelines.¹⁸ A diagnosis of HSV-2 should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2015 CDC Sexually Transmitted Disease Treatment Guidelines.¹⁸ Serologic screening for HSV-1 infection **is not recommended**.

Preventing Exposure

Although most people with HIV also have HSV-1 and HSV-2 infections, it is important to prevent HSV-2 acquisition in those who do not have HSV-2. Persons with HIV who are HSV-2 seronegative should consider asking their partners to be tested using HSV type-specific serology before initiating sexual activity because disclosure of HSV-2 in heterosexual HIV-negative, HSV-2-discordant couples was associated with reduced risk of transmission of HSV-2 (**BII**).¹⁹ Consistent use of latex condoms reduced HSV-2 acquisition among heterosexual couples, and their use should be encouraged to prevent transmission of HSV-2 and other sexually transmitted pathogens (**AII**).^{20,21}

Sexual transmission of HSV most often occurs during episodes of asymptomatic viral shedding. However, persons with HIV should specifically avoid sexual contact with partners who have overt genital or orolabial herpetic lesions (**AII**).

In HSV-2 seropositive persons who have symptomatic genital herpes but not HIV, suppressive antiviral therapy (e.g., valacyclovir 500 mg once daily) reduced HSV-2 transmission to susceptible heterosexual partners by 48%.²² However, in HIV-1/HSV-2-seropositive persons not on antiretroviral therapy (ART), suppressive acyclovir (400 mg twice daily) did not prevent HSV-2 transmission to HSV-2 seronegative partners.²³ Suppressive anti-HSV therapy to prevent HSV-2 transmission to susceptible partners **is not recommended** for persons with HIV/HSV-2 coinfection who are not on ART (**AI**). There are no data available regarding use of suppressive therapy to prevent genital HSV-1 transmission.

Preventing Disease

Prophylaxis with antiviral drugs to prevent primary HSV infection **is not recommended** (**AIII**). In clinical trials, pre-exposure prophylaxis with vaginal tenofovir gel and oral tenofovir disoproxil fumarate (TDF) or with TDF/emtricitabine has been associated with reduced risk of HSV-2 acquisition in persons without HIV.²⁴⁻²⁶ However, HSV-2 seronegative persons with HIV on TDF-containing ART regimens are at similar risk of acquiring HSV-2 as those on non-TDF containing ART regimens, suggesting that TDF is not effective in preventing HSV-2 acquisition in persons with HIV infection.²⁷ The dose, duration, timing, and efficacy of anti-HSV prophylaxis after known or suspected exposure to HSV has not been evaluated. No vaccine for prevention of HSV infection is available. Some studies have shown that medical male circumcision (MMC) decreased the risk of HSV-2 acquisition in African men without HIV,^{28,29} and may be associated with decreased risk of HSV-2 transmission to female partners.³⁰ However, MMC to decrease risk of HSV-2 acquisition and transmission has not been studied among men with HIV and therefore **is not recommended** for the sole purpose of preventing HSV acquisition (**AIII**).

Treating Disease

Patients with HSV infections can be treated with episodic antiviral therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. Acyclovir, valacyclovir, and famciclovir are effective for suppressive and episodic therapy. Valacyclovir is the prodrug of acyclovir, and has improved oral bioavailability, with decreased dosing frequency, compared to acyclovir. When deciding on suppressive therapy for genital HSV-2 infection in persons with HIV and HSV-2 coinfection, factors to consider include the frequency and severity of HSV recurrences and risk for genital ulcer disease (GUD) when initiating ART.³¹ Episodic treatment for individual recurrences of GUD does not influence the natural history of genital HSV-2 infection.

Patients with orolabial HSV lesions can be treated with oral acyclovir, valacyclovir, or famciclovir for 5 days to 10 days (**AIII**). First episodes of genital HSV should be treated with oral acyclovir, valacyclovir, or famciclovir for 7 days to 10 days; recurrences can be treated for 5 to 10 days (**AI**). Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir (**AIII**).^{11,32} Once the lesions begin to regress, patients can be switched to oral antiviral therapy. Therapy should be continued until the lesions have completely healed. Although disseminated disease due to HSV is rare in persons with HIV, HSV necrotizing retinitis can occur, which may be difficult to distinguish clinically from retinitis caused by varicella-zoster virus.

Special Considerations with Regard to Starting Antiretroviral Therapy

Orolabial and genital HSV should not influence the decision on when to start ART in persons with HIV. Transient increases in HSV-2–associated genital ulcers have been observed during the first 6 months after initiation of ART in HIV/HSV-2 coinfecting persons. In such cases, suppressive anti-HSV therapy can be considered. The frequency and severity of clinical episodes of genital herpes is often reduced in individuals after immune reconstitution on ART. However, immune reconstitution does not reduce the frequency of genital HSV shedding.³³

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed for patients receiving episodic or suppressive HSV therapy unless they have advanced renal impairment. However, for patients receiving high-dose IV acyclovir, monitoring of renal function, and dose adjustment as necessary, are recommended at initiation of treatment and once or twice weekly for the duration of treatment.

HSV-2 shedding and GUD can increase in the first 6 months after initiation of ART, particularly in those with low CD4 counts.^{34,35} Mucocutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in individuals initiating ART and have been attributed to immune reconstitution inflammatory syndrome (IRIS).³⁶

Managing Treatment Failure

Treatment failure due to acyclovir resistance should be suspected if herpes-related lesions do not begin to resolve within 7 days to 10 days after initiation of anti-HSV therapy. In persons with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing done to confirm drug resistance (**AII**).³⁷ Phenotypic testing of viral isolates has been the gold standard method for assessing HSV resistance; genotypic testing is not yet available.

The treatment of choice for acyclovir-resistant HSV is IV foscarnet (**AI**).^{38,39} IV cidofovir is a potential alternative (**CIII**). A novel agent, the helicase-primase inhibitor pritelivir, is currently being tested in clinical trials for treatment of acyclovir-resistant herpes in immunocompromised persons (*ClinicalTrials.gov* Identifier: [NCT03073967](https://clinicaltrials.gov/ct2/show/study/NCT03073967)). There is an Expanded Access Program available for oral pritelivir in these populations; for more information see [AiCuris Pritelivir Early Access website](https://www.aicurus.com/pritelivir-early-access). Topical trifluridine, foscarnet,

cidofovir, and imiquimod also have been used successfully to treat external lesions, although prolonged application for 21 days to 28 days or longer may be required (**CIII**).⁴⁰⁻⁴⁴

Preventing Recurrence

Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences of HSV lesions and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences (**AI**).^{14,45} Suppressive therapy for HSV may be continued indefinitely, without regard to improved CD4 count, although the need for continued therapy should be addressed on an annual basis, particularly if immune reconstitution has occurred (**BIII**). Persons starting ART with CD4 counts <250 cells/mm³ have an increased risk of HSV-2 shedding and GUD in the first 6 months on ART. Suppressive acyclovir decreases the risk of GUD nearly 60%, and may be recommended for persons with CD4 counts <250 cells/mm³ starting ART (**BI**).

In persons with HIV not on ART, suppressive anti-HSV therapy also results in a decrease in HIV RNA levels in plasma, anal, and genital secretions, and in a lower risk of HIV progression.⁴⁶ However, antiviral regimens for herpes do not decrease the risk of HIV transmission to sexual partners, and should not be used in place of ART to delay HIV progression.⁴⁷ In persons who are taking ART, suppressive HSV antivirals do not delay HIV progression, improve CD4 recovery, or decrease markers of systemic inflammation^{48,49} and are not useful for these ends (**AI**).

Although there is no data specific to persons with HIV, in hematopoietic stem cell recipients, the risk of developing acyclovir-resistant HSV was lower with daily suppressive acyclovir therapy than with episodic therapy.⁵⁰

Special Considerations During Pregnancy

Laboratory testing to diagnose mucocutaneous HSV infections is the same for pregnant women as for non-pregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy. Visceral disease following HSV acquisition is more likely to occur during pregnancy and can be fatal. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe, particularly during the second and third trimesters (**AIII**).⁵¹ One recent case-control study suggested a higher risk of gastroschisis associated with both genital herpes and acyclovir use during the first trimester of pregnancy.⁵² The use of valacyclovir and famciclovir during pregnancy has been described, and the antiviral drugs also appear to be safe and well tolerated during the third trimester.⁵³ Given its simplified dosing schedule valacyclovir is an option for treatment and suppressive therapy during pregnancy (**CIII**).

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate. The rate of neonatal HSV transmission in HSV-2-seropositive pregnant women is low, except in those who acquire genital HSV infection late in pregnancy. However, when HSV transmission does occur, the adverse sequelae for the neonate can be very significant. The predominant risk for neonatal HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor (**BII**).¹⁴ Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes outbreaks and reduces the need for cesarean delivery for recurrent HSV in HIV-seronegative women⁵⁴ and is likely to have similar efficacy in women with HIV infection. However, neonatal HSV disease has been reported in infants born to women treated with antenatal suppressive antiviral therapy.⁵⁵ Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks' gestation for pregnant women with recurrences of genital herpes during pregnancy (**BII**).⁵⁶ Suppressive therapy for women who are seropositive for HSV-2 but no history of genital lesions **is not recommended**. Maternal genital herpes was a risk factor for perinatal HIV transmission in the era preceding availability of ART.⁵⁷ Whether HSV facilitates HIV transmission in pregnant women on ART is unknown.

Recommendations for Treating Herpes Simplex Virus Infections

Note: Compared to acyclovir, valacyclovir has improved bioavailability and requires less frequent dosing.

Treating Orolabial Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day **(AIII)**, *or*
- Famciclovir 500 mg PO twice a day **(AIII)**, *or*
- Acyclovir 400 mg PO three times a day **(AIII)**

Treating Initial Genital Lesions (Duration: 7–10 Days) or Recurrent Genital Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day **(AI)**, *or*
- Famciclovir 500 mg PO twice a day **(AI)**, *or*
- Acyclovir 400 mg PO three times a day **(AI)**

Treating Severe Mucocutaneous HSV Infections (AIII)

- For initial therapy, acyclovir 5 mg/kg IV every 8 hours
- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

Chronic Suppressive Therapy

Indications:

- For patients with severe recurrences **(AI)**, *or*
- Patients who want to minimize the frequency of recurrences **(AI)**, including pregnant women, *or*
- To reduce the risk of genital ulcer disease in patients with CD4 counts <250 cells/mm³ who are starting ART **(BI)**

Treatment:

- Valacyclovir 500 mg PO twice a day **(AI)**, *or*
- Famciclovir 500 mg PO twice a day **(AI)**, *or*
- Acyclovir 400 mg PO twice a day **(AI)**
- Evaluate ongoing need for suppressive therapy annually.

For Acyclovir-Resistant Mucocutaneous HSV Infections

Preferred Therapy:

- IV Foscarnet 80–120 mg/kg/day in 2–3 divided doses until clinical response **(AI)**

Alternative Therapy (Duration: ≥21–28 Days, Based on Clinical Response) **(CIII)**:

- IV cidofovir 5 mg/kg once weekly, *or*
- Topical trifluridine 1% three times a day, *or*
- Topical cidofovir 1% gel once daily, *or*
- Topical imiquimod 5% cream three times a week, *or*
- Topical foscarnet 1% five times a day

Notes:

- Topical formulations of trifluridine, cidofovir, and foscarnet are not commercially available.
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir and foscarnet.
- An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir-resistant HSV infection; for more information see [AiCuris Pritelivir Early Access website](https://www.aicurus.com/pritelivir-early-access).

Key: ART = antiretroviral therapy; HSV = herpes simplex virus; IV = intravenously; PO = orally

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