Herpes Simplex Virus

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Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common. Among people aged 14 to 49 years in the United States as of 2016, the HSV-1 seroprevalence is 47.8%, and the HSV-2 seroprevalence is 11.9%.[1] Although most cases of recurrent genital herpes are due to HSV-2, HSV-1 has become an increasing cause of first-episode genital herpes, causing up to 42% of infections in young adult heterosexual women and 76% of infections in young adult men who have sex with men in Sydney, Australia between 1992 to 2006.[2] In one study earlier in the HIV epidemic, approximately 60% of people with HIV were HSV-2 seropositive, and 96% were seropositive for either HSV-1 or HSV-2.[3,4] HSV-2 infection increases the risk of HIV acquisition two- to threefold.[5,6] In HIV-1/HSV-2 coinfected people not taking effective antiretroviral therapy (ART), the rate of HSV-2 reactivation and shedding is increased,[7] and HSV-2 reactivation is associated with increased HIV RNA levels in plasma and genital secretions.[8]

Clinical Manifestations

The majority of clinically evident infections with herpes simplex virus (HSV) manifest as mucocutaneous lesions, occurring in either perioral or genital distributions.

Orolabial 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 persons is 5 to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight and physiologic stress.[9]

The majority of individuals with HSV-2 seropositivity have clinically silent infection.[10] Genital herpes is typically caused by HSV-2 and is the most common manifestation of symptomatic HSV-2 infection, though HSV-2 can also cause orolabial herpes. Genital herpes caused by HSV-1 is clinically indistinguishable from HSV-2 infection, although recurrences and viral shedding occur less often with genital HSV-1 infection.[11] Typical genital mucosal or skin lesions evolve through stages of papule to 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, mons pubis, thighs). Local symptoms might include a sensory prodrome consisting of pain and pruritus. Mucosal genital disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.[12] Fever can also occur in primary infection. These classic manifestations occur in some people, 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 people with HIV with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3 than in those without HIV or with higher CD4 counts.[13,14]

HSV-1 and HSV-2 are significant causes of proctitis in men with HIV who have sex with men and may occur in the absence of external anal ulcers.[15] In profoundly immunocompromised people (CD4 counts <100 cells/mm^3), extensive, deep, nonhealing ulcerations can occur. Perirectal HSV lesions are more likely to be resistant to acyclovir compared to lesions at other locations.[16] In addition, atypical presentations, such as hypertrophic genital HSV,[17,18] which mimics neoplasia and requires biopsy for diagnosis, may be seen in people with HIV.

HSV esophagitis presents similarly in people with and without HIV, aside from extended symptom duration.[19] The manifestations of other non-mucocutaneous or disseminated HSV infections (e.g., acute retinal necrosis, keratitis, meningitis, encephalitis, Bell's palsy, hepatitis, herpetic whitlow) are similar to those observed in people without HIV. Disseminated HSV infection is rare, even in profoundly immunosuppressed people, such as recipients of hematopoietic stem cell transplant[20] and solid organ transplant.[21]

Diagnosis

Because mucocutaneous HSV infections cannot be diagnosed accurately by clinical examination alone, a laboratory diagnosis of all suspected HSV mucocutaneous infections should be pursued.[22] HSV DNA polymerase chain reaction (PCR) is the preferred method for mucocutaneous lesions potentially caused by HSV. PCR is the most sensitive method of diagnosis; viral culture sensitivity decreases as lesions heal.[23] Testing for other sexually transmitted infections and infectious causes of ulcerative disease—including varicella zoster virus, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, and mpox—is also advised based on local endemicity and patient risk factors.

For suspected central nervous system (CNS) infection, PCR can be run directly on cerebral spinal fluid specimens. Differentiation between CNS infection with HSV-1 and HSV-2 should be pursued to guide conversations about risk of recurrence. HSV PCR of the blood should not be used to diagnose mucosal HSV unless there is concern for disseminated disease. HSV detected in genital and oral lesions should be tested for both HSV-1 and HSV-2 for purposes of counseling on recurrence and transmission. Testing for other manifestations of HSV (e.g., esophagitis, meningitis, encephalitis, hepatitis, keratitis, etc.) is the same in people with and without HIV.

Type-specific serum and point-of-care immunoglobulin G serologic assays are commercially available and can be used for the diagnosis of HSV-2 infection in asymptomatic individuals or those with atypical lesions. Type-specific serologic screening for HSV-2 can be considered for people with HIV, particularly for those with history of genital ulcer disease, atypical genital lesions that were not confirmed as HSV by PCR or culture, and for those whose sexual partners have HSV-2 infection.[22] However, providers should be aware that there are some important limitations of currently available serologic tests. False negative serologies can occur in early infection; repeat testing 12 weeks following suspected exposure is warranted. False positive HSV-2 serologic test results occur with the enzyme immunoassay antibody tests, particularly at low index values (1.1–3.0).[24-26] In such situations, confirmatory testing with a second serologic test using a different antigen is recommended.[27] Serologic screening for HSV-1 infection is not useful due to high prevalence, and HSV-1 or HSV-2 immunoglobulin M (IgM) is not useful because IgM testing is not type-specific.[22]

A diagnosis of genital herpes should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2021 CDC Sexually Transmitted Infections Treatment Guidelines.

Preventing Exposure

Although earlier in the HIV epidemic most people with HIV were found to also have HSV-1 and HSV-2 infections,[4] more recent prevalence is not known, and preventing HSV-2 acquisition in those who do not already have HSV-2 is important. In heterosexual HIV-negative but HSV-2-serodifferent couples, disclosure of HSV-2 status is associated with reduced risk of HSV-2 transmission.[28] Consistent use of condoms reduces HSV-2 acquisition in heterosexual couples and should be encouraged to prevent transmission of HSV-2 and other sexually transmitted pathogens **(AII).**[29] The association between consistent condom use and the reduction of HSV-2 acquisition in men who have sex with men has not been studied, but consistent condom use should be encouraged **(AIII).**

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

The value of using suppressive antiviral therapy to prevent transmission of HSV-2 might vary according to HIV status. In people with symptomatic HSV-2 without HIV, suppressive antiviral therapy with valacyclovir 500 mg once daily reduced HSV-2 transmission to susceptible heterosexual partners by 48%.[30] However, in people seropositive for HSV-2 and HIV-1 but not taking ART, suppressive acyclovir at 400 mg twice daily did not prevent HSV-2 transmission to HSV-2–seronegative partners.[31] It is unknown if the lack of efficacy in the latter study was related to HIV-1 infection, uncontrolled HIV-1 viremia, the suppressive regimen, or because HSV-2 seropositive patients did not need to have a history of genital ulcer disease to participate. Extrapolating from the HSV-2 transmission trial among people without HIV, use of suppressive anti-HSV therapy used only for the purpose of preventing HSV-2 transmission to seronegative partners can be considered as part of a shared-decision-making conversation with applicable patients and partners particularly if there is a history of genital ulcer disease **(BIII).** Patients should be made aware that this strategy may be of modest benefit in preventing transmission, and other methods of risk reduction should also be considered to maximize protection **(BIII).** There are no data available regarding the 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 people without HIV.[32-34] However, HSV-2 seronegative people with HIV on TDF-containing ART regimens are at similar risk of acquiring HSV-2 as those on non-TDF-containing ART regimens,[35] suggesting that TDF is not effective in preventing HSV-2 acquisition in people with HIV. The dose, duration, timing, and efficacy of anti-HSV prophylaxis after known or suspected exposure to HSV have not been evaluated. No vaccine for prevention of HSV infection is available. Some studies have shown that medical male circumcision decreased the risk of HSV-2 acquisition in African men without HIV,[36,37] and may be associated with decreased risk of HSV-2 transmission to female partners.[38] However, medical male circumcision 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

Recommendations for Treating Herpes Simplex Virus Infections

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

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)

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)

Severe Mucocutaneous and Visceral or Disseminated HSV Infections

- For initial therapy, acyclovir 10 mg/kg IV every 8 hours for 10–14 days (AIII)
- For mucocutaneous lesions, change to oral therapy (dose as above) once lesions begin to regress (AIII); continue oral treatment until lesions have completely healed (AIII)
- Some clinicians will elect to extend the course of treatment for visceral or disseminated disease based on clinical response and degree of immunosuppression.

Ophthalmic HSV Disease

- Consultation with an ophthalmologist experienced in the management of patients with HSV ocular disease is strongly recommended (AIII).

Epithelial Keratitis

- Valacyclovir 1 g PO twice a day for 5–10 days (BIII), *or*
- Acyclovir 400 mg PO 5 times a day for 5–10 days (BIII), *or*
- Trifluridine eye drops: 1 drop in affected eye every 2 hours while awake (maximum nine times per day) until complete re-epithelialization, then 1 drop every 4 hours while awake (minimum five times per day) for an additional 7 days (BIII), *or*
- Ganciclovir 0.15% gel: 1 drop to affected eye five times a day (every 3 hours while awake) until re-epithelialization has occurred; then 1 drop 3 times a day for an additional 7 days (BIII)

Note: Topical steroids are not recommended in the management of active epithelial keratitis (AIII).

Stromal Keratitis (Duration of Antivirals: ≥1 Year)

- Acyclovir 400 mg PO twice a day (AII) *or* valacyclovir 500 mg PO once daily (AIII), *plus*
- Prednisolone 1% 1 drop to affected eye 6–8 times per day for at least 10 weeks followed by taper; exact course should be managed by ophthalmologist based on individual patient course (AIII)

HSV of the Central Nervous System

HSV Meningitis (Duration: 10–14 Days) (AIII)

- For initial therapy, acyclovir 10 mg/kg IV every 8 hours
- After clinical improvement, change to valacyclovir 1 g PO three times a day

HSV Encephalitis (Duration: 14–21 Days) (CIII)

- Acyclovir 10 mg/kg IV every 8 hours
- Some clinicians will elect to extend the course based on clinical response and degree of immunosuppression.

Treatment of Acyclovir-Resistant Mucocutaneous HSV Infections

Treatment failure due to acyclovir resistance should be suspected if lesions do not begin to resolve within 7–10 days after initiation of anti-HSV therapy. All acyclovir-resistant strains are also resistant to valacyclovir, and most are resistant to famciclovir.

Treatment of acyclovir-resistant HSV should be given in consultation with an infectious disease expert (AIII).

Preferred Therapy

- IV foscarnet 40 mg/kg every 8–12 hours until clinical response (AI)

Alternative Therapy

- Topical imiquimod 5% cream three times a week (BIII), *or*
- Topical cidofovir 1% gel once daily (BIII), *or*
- Topical trifluridine 1% three times a day (BIII), *or*
- Topical foscarnet 1% five times a day (BIII), *or*
- IV cidofovir 5 mg/kg once weekly for 2 weeks, then every other week (CIII)
  - Administer probenecid 2 g PO 3 hours before each cidofovir dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g). Administer 1 L of normal saline before and, if additional fluid load can be tolerated, administer another 1 L of normal saline after each cidofovir infusion.
  - Note: Cidofovir should be avoided in patients with sulfonamide allergy because of cross-hypersensitivity with probenecid.

Duration

- Based on clinical response; typically 21–28 days or longer

Notes

- An expanded access program of oral pritelivir is available for immunocompromised people with acyclovir-resistant HSV infection; see the Managing Treatment Failure in Mucocutaneous Disease section for more information.
- 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.
- Recurrences following episodes of acyclovir-resistant HSV can be caused by either acyclovir-resistant or acyclovir-sensitive strains; after resolution of the acyclovir-resistant episode, suppressive therapy with acyclovir can be considered to prevent additional recurrences (CIII).

Pregnancy Considerations

- Acyclovir is an option for treatment during pregnancy, including during the first trimester (AII).
- Given its simplified dosing schedule, valacyclovir is also an option for treatment during pregnancy (BII).

Key: HSV = herpes simplex virus; IV = intravenous; PO = oral

People 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 all effective for suppressive and episodic therapy. Valacyclovir is a prodrug of acyclovir, and famciclovir is a prodrug of penciclovir (only available topically); both have improved oral bioavailability and allow for decreased dosing frequency compared to acyclovir, making them preferred oral regimens for patient dosing convenience and adherence, if available. Episodic treatment for individual recurrences of genital ulcer disease does not influence the natural history of genital HSV-2 infection.

People with orolabial HSV lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5 to 10 days **(AIII).** First episodes of genital HSV lesions should be treated with oral valacyclovir, famciclovir, or acyclovir for 7 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 for 10 to 14 days **(AIII).**[16,39] Once the lesions begin to regress, those being treated can be switched to oral antiviral therapy **(AIII).** Therapy should be continued until the lesions have completely healed **(AIII).**

HSV infections of the corneal epithelium (epithelial keratitis) are due to active viral infection and should be treated with oral valacyclovir 1,000 mg twice daily or acyclovir 400 mg five times daily for 5 to 10 days, or with a topical antiviral agent until resolution of dendritic lesions and re-epithelialization **(BIII).** Treatment by either route is effective; use of both oral and topical agents in combination is not necessary.[40] For topical treatment, ophthalmic trifluridine drops **(BIII)** or ganciclovir gel **(BIII)** can be used, though there are limitations to each. While it is not expected that treatment would be required beyond 2 weeks, using trifluridine beyond this time frame may result in toxicity to the corneal epithelium; ganciclovir can be cost prohibitive. Acyclovir ophthalmic ointment is also an appropriate option but is not currently available in the United States. Topical steroids are not recommended in the management of active epithelial keratitis **(AIII).**

For patients who also have stromal keratitis, largely due to inflammation rather than replicating virus, topical steroids are the mainstay of treatment. Prednisolone 1% eye drops (1 drop to affected eye 6–8 times a day) is given for at least 10 weeks, followed by a slow taper. Steroids should be given in conjunction with acyclovir 400 mg twice daily **(AII)**[41] or valacyclovir 500 mg daily **(AIII)** for at least one year to decrease the risk of recurrent stromal inflammation. Topical antivirals should not be used for extended durations to prevent recurrence, as this can cause toxicity to the eye that can be confused with persistent infection. As HSV keratitis exists along a continuum between epithelial viral replication and stromal inflammation, all cases should be managed by an ophthalmologist **(AIII).** Management is focused on striking a balance between viral clearance, control of inflammation, and prevention of reactivation.

For HSV meningitis, initial treatment with acyclovir IV 10 mg/kg every 8 hours is recommended, with step-down to high-dose oral valacyclovir 1 g three times daily following clinical improvement, for a total duration of 10 to 14 days **(AIII).**

People with visceral or disseminated HSV disease should be treated with acyclovir 10 mg/kg IV every 8 hours for at least 10 to 14 days **(AIII);** those with HSV encephalitis should be treated with acyclovir 10 mg/kg IV every 8 hours for at least 14 to 21 days **(CIII).** Some clinicians will elect to extend the course based on clinical response and degree of immunosuppression.

Special Considerations Regarding Antiretroviral Therapy Initiation

Orolabial and genital HSV should not influence the decision to start ART in people 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 coinfected people, particularly in those with low CD4 counts.[42,43] In such cases, suppressive anti-HSV therapy can be considered. The frequency and severity of clinical episodes of genital herpes are often reduced in individuals after immune reconstitution on ART. However, immune reconstitution does not reduce the frequency of genital HSV shedding.[44]

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 people receiving episodic or suppressive HSV therapy unless they have advanced renal impairment. However, for people receiving IV acyclovir, cidofovir, or foscarnet, monitoring of renal function and dose adjustment as necessary is recommended at initiation of treatment and at least once or twice weekly for the duration of treatment, if stable (see Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections that Require Dosage Adjustment in Adults With Renal Insufficiency for renal dosing information and the Cytomegalovirus Disease chapter for additional foscarnet and cidofovir monitoring recommendations).

See Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections for additional information on adverse drug reactions.

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).[45]

Managing Treatment Failure in Mucocutaneous Disease

Treatment failure due to acyclovir resistance should be suspected if herpes-related lesions do not begin to resolve within 7 to 10 days after initiation of anti-HSV therapy. Risk factors for acyclovir-resistant HSV include prolonged use of acyclovir, suboptimal acyclovir dosing, immunosuppression, and ongoing HSV replication.[46]

In people with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing should then be conducted to confirm drug resistance **(AII).**[47] Phenotypic testing of viral isolates has been the gold-standard method for assessing HSV resistance; genotypic testing is not widely available but may available at the University of Washington Department of Laboratory Medicine and Pathology.

All acyclovir-resistant strains are also resistant to valacyclovir, and the majority are resistant to famciclovir. Therefore, the treatment of choice for acyclovir-resistant HSV is IV foscarnet **(AI).**[48,49] IV cidofovir is a potential alternative **(CIII).** Systemic foscarnet and cidofovir are nephrotoxic medications; treatment should be given in consultation with an infectious diseases specialist **(AIII)** and with frequent laboratory monitoring (see Table 5).[50] Topical imiquimod, cidofovir, trifluridine, and foscarnet also have been used successfully to treat external lesions **(BIII),** although prolonged application for 21 to 28 days or longer may be required. Topical cidofovir, foscarnet, and trifluridine must be compounded in a pharmacy.[51,52]

A novel oral agent, the helicase-primase inhibitor pritelivir, is currently being tested in clinical trials for treatment of acyclovir-resistant HSV in immunocompromised people (*ClinicalTrials.gov* Identifier: NCT03073967). There is an Expanded Access Program available for oral pritelivir in these populations (also see *ClinicalTrials.gov* Identifier: NCT05844436 for more information).

Preventing Recurrence of Mucocutaneous Disease

Recommendations for Preventing Recurrence of Mucocutaneous Disease
Chronic Suppressive Therapy
Indications • For people with severe or frequent recurrences (AI), *or* • For people who want to minimize the frequency of recurrences (AI), *or* • To reduce the risk of genital ulcer disease in people with CD4 counts <250 cells/mm^3 who are starting ART (BI) Preferred Therapy • Valacyclovir 500 mg PO twice a day (AI) Alternative Therapy • Acyclovir 400 mg PO twice a day (AI), *or* • Famciclovir 500 mg PO twice a day (AI), *or* • Valacyclovir 500 mg or 1,000 mg PO once a day (CIII) o Valacyclovir 500 mg daily is less likely to be effective in people with ≥10 recurrences per year. o Valacyclovir 1,000 mg daily can be considered in people with HIV with more preserved immunologic functioning if they are unable to adhere to twice-daily dosing. Note: In people with prior acyclovir resistance, suppressive acyclovir therapy should be offered after resolution of the episode (CIII). See text below for more information. Duration • May be continued indefinitely, without regard to improved CD4 count; however, the need for continued therapy should be re-evaluated at least annually, particularly if immune reconstitution has occurred (BIII).
Pregnancy Considerations
• Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks gestation for pregnant women with past genital herpes (AI). • Suppressive therapy for pregnant women who are seropositive for HSV-2 but without history of genital lesions is not recommended (BIII).

- Due to increased renal clearance, the recommended dose of acyclovir used for suppressive therapy for HSV infection in pregnancy is 400 mg three times a day (AII).
- Given its simplified dosing schedule, valacyclovir 500 mg twice a day is an option for suppressive therapy during pregnancy (BII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HSV = herpes simplex virus; IV = intravenous; PO = oral

Suppressive therapy reduces the frequency of recurrences of HSV lesions by nearly 80% and improves quality of life.[53] 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 when initiating ART.[44] Suppressive therapy should be offered to people who have severe or frequent HSV recurrences **(AI)** or who want to minimize the frequency of recurrences **(AI).**[22,54] Suppressive therapy may also be offered to those with CD4 counts <250 cells/mm^3 who are initiating ART due to the increased risk of herpes outbreaks after ART initiation **(BI).**

Oral acyclovir, valacyclovir, and famciclovir are all effective; selection of a suppressive antiviral is often based largely on convenience of dosing, making valacyclovir a preferred option by patients.[50] Valacyclovir can be given at 500 mg twice daily **(AI),** 500 mg once daily **(CIII)**, or 1,000 mg once daily **(CIII)** for suppression. The 500-mg daily dose is less likely to be effective in people with 10 or more recurrences per year.[55] Valacyclovir 500 mg twice daily is the only dose specifically studied in people with HIV.[54] Valacyclovir 1,000 mg daily can be considered in people with HIV with more preserved immune function if they are unable to adhere to twice-daily dosing. Oral acyclovir 400 mg twice a day and oral famciclovir 250 mg twice a day are also acceptable options for suppressive therapy **(AI).** Suppressive therapy for HSV may be continued indefinitely, without regard to improved CD4 count, although the need for continued therapy should be addressed at least annually, particularly if immune reconstitution has occurred **(BIII).**

People with HIV are less likely to experience acyclovir-resistant HSV than hematopoietic stem cell recipients.[46,48] With the latter population, the risk of developing acyclovir-resistant HSV was lower with daily suppressive acyclovir therapy than with episodic therapy.[56] Recurrences following episodes of acyclovir-resistant herpes can be caused by either acyclovir-resistant or acyclovir-sensitive strains.[48] Therefore, even in people with prior acyclovir resistance, suppressive acyclovir therapy should be offered after resolution of the episode **(CIII).** It is not expected, however, that acyclovir resistance will wane during a clinical episode, and thus acyclovir should not be used as until resolution of the episode in this setting. If a person with prior acyclovir resistance develops a recurrence while taking acyclovir suppressive therapy, susceptibility testing should be done.

In people with HIV who are not taking effective ART, suppressive anti-HSV therapy decreases HIV RNA levels in plasma, anal, and genital secretions, as well as lowers risk of HIV progression;[57] however, suppressive anti-HSV medications should not be used in place of ART to delay or reduce the risk of HIV progression **(AIII).** In people who are taking ART, suppressive HSV antivirals do not delay HIV progression, improve CD4 recovery, or decrease markers of systemic inflammation[58,59] and are not useful for these outcomes.

Special Considerations During Pregnancy

Laboratory testing to diagnose mucocutaneous HSV infections is the same during pregnancy as for other people with HIV. During pregnancy with primary HSV disease, antiviral therapy should be administered orally for 7 to 10 days (or longer, if lesions are incompletely healed) to reduce the

duration and severity of the symptoms and to reduce the duration of viral shedding. For treatment of severe genital HSV infections or disseminated infections, IV acyclovir may be administered during pregnancy. Pregnant women with recurrent outbreaks should also be given antiviral treatment to reduce symptoms and viral shedding.[22]

Disseminated disease, such as HSV hepatitis, is rare but may be more likely to occur in pregnancy and can be fatal;[60,61] providers should consider disseminated HSV in the differential diagnosis of patients with appropriate clinical and laboratory presentations. Acyclovir is the antiviral drug with the most reported experience in pregnancy, and both animal and human data suggest it is safe in pregnancy, including in the first trimester **(AII).**[62] Due to increased renal clearance in pregnancy, the recommended dose of acyclovir used for suppressive therapy is 400 mg three times daily, higher than the corresponding dose in nonpregnant people.[63] Valacyclovir is rapidly converted to acyclovir after hepatic metabolism and has a safety profile similar to acyclovir;[63] given its simplified dosing schedule, valacyclovir is an option for treatment and suppressive therapy during pregnancy **(BII).** There are limited data on the use of famciclovir during pregnancy.

A case–control study suggested a higher risk of gastroschisis associated with both genital herpes and acyclovir use during the first trimester of pregnancy.[64] The use of valacyclovir and famciclovir during pregnancy has been described, and these antiviral drugs also appear to be safe and well tolerated during the first trimester.[63] Cidofovir is teratogenic and should not be used during pregnancy **(AIII).**

An important concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate, which can result in serious adverse events, including death or long-term neurologic sequelae. Transplacental transmission may occur in very rare cases, resulting in congenital infection, including microcephaly, hepatosplenomegaly, intrauterine growth restriction, and stillbirth; however, most neonatal herpes is acquired during the intrapartum period through exposure to the virus in the maternal genital tract, especially in the presence of active lesions. Approximately one-third to one-half of cases of neonatal herpes are caused by HSV-1.[65,66]

The rate of neonatal HSV transmission is highest with primary HSV-1 or HSV-2 genital infection during late pregnancy.[67] Cesarean delivery is recommended for pregnant women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor **(AII).**[22] Risk of neonatal transmission is reduced in previously HSV-2–seropositive pregnant women or those with prior genital episodes. Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks gestation for pregnant women with past genital herpes **(AI).** Although neonatal HSV disease has been reported in infants born to women treated with antenatal suppressive antiviral therapy,[68] it has been shown to reduce the risk of both asymptomatic shedding as well as clinical recurrence of HSV at the time of delivery and need for cesarean birth.[66,69] For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered. All of these interventions are likely to be similarly effective in people with HIV as in those without. Suppressive therapy for pregnant women who are seropositive for HSV-2 but without history of genital lesions **is not recommended (BIII).** Postnatal transmission can occur rarely. To prevent postnatal transmission, pregnant women with herpetic lesions on any part of the body should take special precautions with handwashing prior to handling the neonate. Maternal genital herpes was a risk factor for perinatal HIV transmission in the pre-ART era.[70] Whether HSV facilitates HIV transmission in pregnant women taking effective ART is unknown.

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