Herpes Simplex Virus – Genital

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Section 1: Pathogen-Based Diseases
Topic 8: Herpes Simplex Virus – Genital

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Epidemiology in the United States

Background and Burden of Disease

Genital herpes is the leading cause of genital ulcer disease worldwide. Both herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) cause genital infection.[1] However, HSV-2 is the more common cause of recurrent genital herpes. Despite a decline in the seroprevalence of HSV-2 from 21.2% in 1988 to 1994 to 15.5% in 2007 to 2010, genital herpes is among the most prevalent sexually transmitted infections in the United States, with approximately 50 million people infected.[2] Based on data from the National Disease and Therapeutic Index, initial visits to physicians’ offices related to genital herpes increased overall during 1966 to 2011, with approximately 300,000 visits in 2014 (Figure 1).[3] In 2008, the lifetime direct medical cost for persons with HSV-2 in the United States was estimated at $540 million. This was significantly higher than the cost estimates for gonorrhea, syphilis, and trichomoniasis combined.[4,5]

Risk Factors for Genital HSV-2 Infection

Investigators have identified multiple risk factors for HSV-2 seropositivity, including female sex, black race, older age, and increasing number of lifetime sex partners.[2,6,7,8,9] In the National Health and Nutrition Examination Survey (NHANES) 2007 to 2010, HSV-2 seroprevalence was 2-fold higher in women (20.3%) compared with men (10.6%) and rates for both men and women were significantly higher in blacks than whites (Figure 2).[2] Data from NHANES shows racial disparities for HSV seroprevalence rates have steadily increased since 1988 and for the most recent time period (2007 to 2010), black females had 3.3 times the HSV seroprevalence rate of white females, and black males had 4.4 times the prevalence rate of white males (Figure 3).[2,9] The correlation of HSV-2 seroprevalence with age is shown by HSV-2 seroprevalence rates of 1.5% among 14 to 19 year-olds to 25.6% among 40 to 49 year-olds; the seroprevalence rates rapidly rise in 20 to 29 year olds.[2] In an earlier NHANES, HSV-2 seroprevalence rates were 3.8% among those who reported one lifetime sex partner, 20.8% among those with 5 to 9 lifetime sex partners, and 39.9% of those with 50 or more lifetime partners.[6]

Risk Factors for Genital HSV-1 Infection

First-episode genital herpes caused by HSV-1 has increasingly been identified among young women, college students, and men who have sex with men (MSM).[8,10,11,12,13] Acquisition of genital HSV-1 can occur through genital-genital contact or via receptive oral sex.[14,15] In some settings, such as university campuses, HSV-1 has now replaced HSV-2 as the leading cause of first-episode genital herpes.[11] One proposed reason for this shift is decreasing HSV-1 orolabial infection in childhood and early adolescence,[8] with first exposure to HSV-1 occurring later in life with sexual activity. Changing sexual practices in young
adults, namely an increase in oral-genital sex, may also contribute to the changing epidemiology of genital herpes.
Microbiology and Pathogenesis

Viral Structure

Both types of HSV are 150 to 200 nm alphaherpesviruses (Figure 4) that are structurally comprised of four major components: DNA, capsid, tegument, and lipid envelope (Figure 5).[16,17] The HSV genome is a single, linear molecule of double-stranded DNA (approximately 152,000 base pairs that encode at least 74 genes); the DNA genome is encased in an icosahedral capsid, also referred to as the viral core, which consists of 162 subunit capsomeres. The tegument, also referred to as the matrix, is an amorphous protein-rich layer that surrounds the capsid. The envelope makes up the outermost part of HSV and consists of a lipid bilayer membrane studded with an array of 12 distinct types of glycoproteins. The glycoproteins are required for viral entry and elicit neutralizing antibodies. Efforts to develop an HSV vaccine, have targeted the envelope glycoproteins, but thus far have been unsuccessful.[18] In addition, differences in glycoprotein G (gG) between HSV-1 and HSV-2 have been exploited for development of type-specific serologic testing.[19,20] At the nucleotide level, HSV-1 and HSV-2 are approximately 50% homologous and about 80% on the amino acid level.

Viral Latency

During initial infection, HSV penetrates susceptible mucosal surfaces or abraded cracks in the skin. The virus is transported from epithelial cells to nerve endings and then along peripheral nerve axons through retrograde transport where HSV establishes persistent infection as an episome in the nerve cell bodies in the sacral ganglia and paraspinous ganglia.[21] In the ganglia, HSV enters a “latent” state with expression of viral microRNAs and the latency-associated transcript-factors that are important for prevention of neuronal apoptosis, maintenance of latency, and regulation of spontaneous viral reactivation.[22,23,24,25] Because HSV is not cleared from neurons, the ganglia become lifelong reservoirs of virus.

Viral Reactivation

The steps leading to the transition between latent infection and lytic replication are poorly understood. In vitro studies have shown that viral reactivation can be induced by neuronal stress, as may occur through interruptions in signaling of neurotrophic factors.[26] This early viral reactivation leads to transcription of the immediate early (IE) viral genes, despite the presence of repressive histone modifications to viral DNA. Early and late viral genes are then transcribed, and proteins such as the viral protein 16 (VP16) lead to chromatin remodeling.[27,28] Such modifications are thought to allow for DNA replication, transcription/translation of viral proteins, and subsequent viral transport down the axon to epithelial cells. In the epithelial cells, bursts of viral replication occur, leading to either asymptomatic viral shedding or clinically symptomatic genital ulcer disease. Of note, genital HSV recurrences can occur throughout the distribution innervated by the sacral ganglia, including the buttocks and thighs. It is important to note that although genital herpes lesions occur in circumscribed areas, viral shedding is more diffuse and can be detected throughout the genital region.[29,30]

Dynamics of Viral Shedding

Although HSV was previously thought to be in a latent state, or “off”, most of the time, more intensive shedding studies involving sampling multiple times per day have revealed that shedding episodes are frequent and approximately 60% of the episodes are less than 24 hours in duration (median 13 hours) (Figure 6).[31] Mathematical modeling studies suggest that latency is much more dynamic, with small quantities of virus released from the ganglia on most days.[32] Tissue resident memory CD8+ T cells, which are located in genital tissue, are thought to rapidly contain viral shedding.[33,34] The frequent viral shedding and primed host immune response may contribute to the increased genital tract inflammation noted in persons with HSV-2 infection.[35] In addition, HSV-2 reactivation selectively recruits CD4 cells (HIV target cells) to the genital skin and mucosa and likely account for the increased risk for HIV acquisition in HSV-2 seropositive persons.[36,37,38]
Asymptomatic Viral Shedding

Studies of HSV-2 seropositive persons have documented that most have asymptomatic viral shedding.[39, 40] Asymptomatic shedding of HSV in women most often occurs from the vulva and perianal area whereas in men it occurs from the penile skin and perianal area.[40, 41] Asymptomatic viral shedding is shorter in duration than shedding during clinical recurrences, but the quantity of virus shed is similar in symptomatic and subclinical episodes.[39] The percentage of days with asymptomatic HSV-2 genital shedding is highest in the first year after infection and gradually decreases over time, though even after 10 years of infection the shedding remains relatively frequent, with shedding detected on about 17% of days.[42, 43] The majority of HSV-2 transmission is thought to occur with viral shedding in asymptomatic persons.[42, 44, 45] Antiviral suppressive therapy dramatically reduces HSV-2 shedding by 70 to 80%, but it does not eradicate it.[29, 46] Genital HSV-1 shedding is less frequent than HSV-2 shedding, with shedding detected by culture on 2% of days.[29, 41, 47, 48]

Transmission of HSV

Transmission of HSV usually occurs through close contact with a person who is shedding virus at a mucosal or epithelial surface, or in genital or oral secretions. Sexual transmission of HSV-1 and HSV-2 can occur through genital-to-genital, oral-to-genital, or genital-to-oral contact. The transmission of HSV-2 most often involves asymptomatic shedding of HSV-2, often in persons unaware that they have HSV infection.[42, 44, 45, 49] The relative efficiency of sexual transmission is thought to be greater from men-to-women than from women-to-men.[41] In addition, HSV can be transmitted perinatally (mother-to-child) at the time of delivery through direct mucosal or skin contact. Fomite transmission of HSV is unlikely, although autotransmission of viral particles can occur from genital sites to other mucocutaneous sites, fingers, or eyes.[50]
Clinical Manifestations

Types of Genital HSV Infection

The clinical manifestations of herpes infection vary significantly when comparing first clinical episode and recurrent outbreaks. The severity and frequency of clinical manifestations, and the recurrence rate, are influenced by viral type (HSV-1 versus HSV-2) and immune status of the host. Investigators have shown that strong HSV-specific T-cell responses during primary genital infection correlate with lower numbers of recurrences in subsequent years.[34] Women tend to have more severe disease characterized by more systemic symptoms when compared with men.[51,52] The incubation period between HSV acquisition and onset of symptoms is, on average, 4 days (range 2 to 12 days). Reactivation induces viral replication and is precipitated by multiple known factors (trauma, fever, ultraviolet light, physical or emotional stress, immunosuppression, fatigue, menses, sexual intercourse) as well as unknown factors.[51,53] HSV causes a wide spectrum of disease depending on whether the infection is a primary, nonprimary (infection with HSV-1 or HSV-2 in an individual with pre-existing antibodies to the other virus), or a recurrent episode.

First Clinical Episode

The first clinical episode refers to the initial symptomatic occurrence of genital herpes. The first clinical episode with HSV-1 or HSV-2 can occur (a) at the time of primary infection (absence of antibody to HSV-1 and HSV-2), (b) at the time of non-primary infection (presence of HSV-1 or HSV-2 antibody with acquisition of the other viral type), or (c) with a symptomatic outbreak of HSV in a person with prior asymptomatic acquisition of the same viral type. Approximately 25% of patients who present with a first clinical episode of HSV-2 have a positive HSV-2 antibody test, consistent with previous unrecognized or asymptomatic acquisition of HSV-2.[52]

Primary Genital Infection

Primary infection is defined as the first infection with either HSV-1 or HSV-2 with absence of antibody to either HSV type. Primary genital infection is often symptomatic, but patients may have unrecognized or subclinical infection. With symptomatic infection, clinical manifestations of primary infection typically resolve within 3 weeks in the absence of antiviral therapy. Serum antibodies appear within 12 weeks of the primary infection in most persons.[54] The following symptoms may occur with primary HSV-1 or HSV-2 genital infection:

- Severe multiple bilateral genital ulcers, pain, itching, dysuria, vaginal or urethral discharge, and tender inguinal adenopathy (Figure 7).
- Without antiviral therapy, lesions last 2 to 3 weeks, with evolution of the lesions from vesicle pustule to wet ulcers to dry crusts (Figure 8).[55]
- The median duration of viral shedding is about 10 to 12 days, and correlates with the time from the onset of vesicles to crusting of lesions.[56]
- Systemic symptoms (fever, myalgias, headaches, aseptic meningitis or symptoms of autonomic nervous system dysfunction such as urinary retention) peak within 3 to 5 days of onset of lesions and gradually recede over the next 3 to 4 days.[57]
- In women, HSV shedding from the cervix occurs in 80 to 90% of primary HSV-1 and HSV-2 infections.[52] Cervicitis may involve the ectocervix or endocervix, with or without clinical symptoms. In most cases, the cervix appears abnormal to inspection with ulcerative lesions, erythema, or friability.
- Herpes proctitis typically manifests with fever, pain, discharge, tenesmus, and constipation; some patients will have severe anal ulcerations visible on anoscopy; some patients develop symptoms of autonomic dysfunction, including difficulty urinating.[58] Rarely, herpes proctitis may present as a pseudotumor that mimics epidermoid carcinoma.[59]
- Infection of the urethritis and/or meatus may cause a clear mucoid discharge.[60]
Nonprimary Infection

The term nonprimary HSV infection most often refers to infection with HSV-1 or HSV-2 in an individual with pre-existing antibodies to the other virus. For example, a person may acquire oral HSV-1 infection as a child and later acquire genital HSV-2 as an adult. Manifestations of nonprimary infection tend to be milder than those of primary infection, presumably due to cross-immunity protection from prior infection with the other HSV type.[61, 62] Less often, in a different scenario, nonprimary infection can occur when a person has asymptomatic HSV-2 acquisition with development of antibody to HSV followed later by a symptomatic outbreak.

Recurrent Symptomatic Infection

This refers to genital HSV recurrences in the setting of a known diagnosis of genital HSV. Recurrent symptomatic infection is characterized by a shorter, milder illness, typically with unilateral lesions that resolve within 3 to 5 days of onset. Lesions typically progress from vesicle pustule (Figure 9) to dry ulcer (Figure 10) to wet ulcer (Figure 11), but the progression is condensed compared with initial infection (Figure 12). Patients with recurrent symptomatic infection generally do not develop systemic symptoms. For HSV-2, the frequency of symptomatic genital herpes reaction decreases after the first year of infection, from a median of 4 to 5 recurrences per year to 3 to 4 recurrences per year; by comparison, for genital HSV-1, the frequency of symptomatic genital herpes is a median of 1 per year during the first year to 0 per year subsequently.[63] Prodromal symptoms (localized tingling, burning) due to HSV traveling along the nerve axons are common and begin 12 to 24 hours before the appearance of lesions. In addition, the number of subsequent episodes of symptomatic infection is higher in women than in men and in persons with prolonged symptoms associated with primary infection.[47, 51, 64]

Unrecognized and Asymptomatic Infection

Approximately 80% of persons seropositive for HSV-2 have never received a diagnosis of genital HSV.[65] Among the 80% of HSV-2 seropositive persons who have undiagnosed genital HSV, an estimated 20% have true asymptomatic infection (or occurrence of genital lesions in locations, such as the cervix, that are not observed) and the remaining 60% have symptoms that are very mild or not recognized (by a clinician or the individual) as being caused by HSV.[66] In addition, some symptoms caused by HSV may be mistaken for another disorder, such as a vaginitis, hemorrhoids, or an allergic reaction.[66] When asymptomatic HSV-2 seropositive individuals receive education about the myriad of symptoms caused by genital HSV infection, approximately two-thirds will subsequently identify symptoms that are consistent with genital HSV-2 infection.[40] Initial HSV-2 genital infection in persons with previous HSV-1 antibodies is often asymptomatic. Persons seropositive for HSV-2 who are unaware of their genital infection account for the majority of transmitted genital HSV infections.[42, 44] Clinicians should inform and educate patients with "asymptomatic infection" about clinical signs and symptoms of genital herpes, as this may help them recognize the subtle manifestations of symptomatic infection (Figure 13).

Complications of Genital HSV Infection

Aseptic meningitis is a well-established potential complication of genital HSV infection, and the majority of cases of HSV-associated aseptic meningitis occur at the time of primary HSV infection. Overall, HSV accounts for up to 10% of all cases of aseptic meningitis, with most of these cases occurring with HSV-2 infection and in women.[61, 67] Aseptic meningitis caused by HSV may be severe, often requiring intravenous antiviral therapy for HSV, hospitalization, and pain control. Permanent neurologic sequelae generally do not result from HSV-associated aseptic meningitis. Uncommon complications of genital HSV infection include benign recurrent lymphocytic meningitis (Mollaret’s meningitis), radicular pain, sacral paresthesias, transverse myelitis, autonomic dysfunction, rectal pseudotumor, disseminated (viremic) infection and fulminant hepatitis.[55, 59, 68]
Genital HSV Manifestations in Persons with HIV Infection

Nearly 60% of persons with HIV infection are coinfected with HSV-2, a seroprevalence for HSV-2 that is three times higher than the general United States population.\[69]\) When compared with HIV-negative individuals, persons with HIV infection tend to have more severe and chronic HSV lesions, as well as more asymptomatic shedding of HSV-2 in the genital tract, particularly when they have advanced immunosuppression.\[70]\) Treatment of HIV infection with effective antiretroviral therapy can reduce the frequency of symptomatic HSV lesions but does not significantly impact HSV-2 mucosal shedding.\[71]\) In addition, the frequency of HSV-2 mucosal shedding has been shown to transiently increase after initiating antiretroviral therapy, likely due to immune reconstitution inflammatory syndrome.\[72,73]\) Unusual ulcerative lesions can also present as a manifestation of immune reconstitution syndrome.\[70]\) In addition, individuals with a CD4 count less than 100 cells/mm\(^3\) may have deep, extensive and non-healing ulcers and may develop acyclovir-resistant HSV if they receive multiple courses of treatment for herpes.\[74,75,76]\)

Genital HSV-2 Infection and Risk of HIV Infection

Genital HSV-2 infection facilitates both acquisition and transmission of HIV. The risk of acquiring HIV increases by at least two-fold in persons with HSV-2 infection, through direct and indirect mechanisms.\[77]\) Unfortunately, HSV suppressive therapy has not been shown to reduce HIV acquisition or transmission.\[78,79]\) For persons who have dual infection with HIV and HSV-2 (and are not taking antiretroviral therapy), HIV can be present in genital herpes ulcerations and HSV-2 reactivation can increase the rates of HIV transcription, resulting in increased HIV RNA levels in both plasma and genital tissues; in contrast, persons on suppressive antiretroviral therapy would expect to have negligible changes in genital and plasma HIV RNA levels associated with HSV outbreaks.\[80,81,82,83]\)

Neonatal Herpes

Neonatal herpes infection is a rare complication of maternal genital herpes infection, occurring in about 1 in 3,200 deliveries in the United States—it is most likely to occur in women who acquire primary genital herpes infection and thus lack maternal antibody at or near the time of delivery.\[84,85]\) In pregnant women with a previous history of HSV-2, the risk of maternal transmission of HSV to the infant is exceedingly low (22/100,000), presumably due to protection conferred by transplacental type-specific HSV antibodies.\[86]\) The majority of cases (85%) of vertical HSV transmission occur during labor and delivery, with only 5% occurring in utero and 10% occurring in the postpartum period.\[84]\) Neonatal herpes is classified as skin, eye, and/or mouth (SEM), disseminated, or central nervous system (CNS) disease. Approximately 70% of infected neonates will develop skin lesions, and disseminated disease may involve multiple organ systems, including the liver, lungs and CNS. The presentation of CNS disease can range from nonspecific symptoms such as lethargy, poor feeding, and temperature instability to encephalitis and seizures.\[84,87]\)
Laboratory Diagnosis

The clinical diagnosis of genital HSV is challenging because many patients do not develop the characteristic vesicular or ulcerative lesions, and less typical lesions, such as fissures, can mimic other infections. Also, physical examination cannot distinguish between disease caused by HSV-1 and HSV-2. Since the natural history and subsequent clinical course depends on whether HSV-1 or HSV-2 is the causative agent, the clinical diagnosis of genital herpes should be confirmed by laboratory testing, including HSV typing.\[10,47,49\] Viral cell HSV culture or nucleic acid amplification methods, including polymerase chain reaction (PCR) assays for HSV DNA, are the preferred HSV tests for persons with genital ulcers or other mucocutaneous lesions. For all samples collected from a lesion, the clinician should obtain an adequate quantity of cells by scraping the base of the lesion; obtaining lesion fluid for diagnostic purposes has low yield since HSV is an intracellular virus. Vesicles, if present, should be unroofed and the base of the ulcer swabbed to obtain adequate cells for viral culture or PCR.

Virologic Tests

Two types of HSV virologic tests are recommended in the 2015 CDC STD Treatment guidelines: PCR and viral culture. For patients with active clinical lesions, the virologic tests offer a significant advantage over serologic tests, in that identification of HSV in the clinical sample confirms the cause of the clinical lesion and allows for HSV typing.

Polymerase Chain Reaction (PCR)

The PCR assays for HSV DNA have very high sensitivity (four-fold higher sensitivity than viral culture) and several tests are now FDA-approved for testing of anogenital specimens.\[88,89\] Use of PCR increases the overall HSV detection rate by 24% when compared with culture.\[90\] In addition, most commercially available PCR assays can differentiate HSV-1 from HSV-2 infection. For patients with suspected HSV central nervous system (CNS) infection, PCR is the preferred test for detecting HSV in cerebrospinal fluid.\[91\]

Viral Culture

Prior to the availability of PCR, viral culture was the gold standard for virologic HSV diagnosis. Viral culture is highly specific, but sensitivity depends on the stage of the lesion and proper collection technique at the time of specimen collection, with the yield declining rapidly as lesions begin to heal. During primary infection, the yield for viral isolation is approximately 80% for early vesicles, 70% for ulcers, and 25% for crusted lesions; for patients with recurrent infection, HSV is isolated in only 25% to 50% of lesions.\[92\] Most cultures will show cytopathic effect (providing indirect evidence of HSV infection) within 24 to 72 hours, but maintaining the viral culture sample in an attempt to isolate HSV is recommended since other viruses may cause a similar cytopathic effect, and isolation of HSV allows for determination of viral typing.\[92\]

Antigen Detection

The use of direct fluorescent antibody (DFA) testing offers lower sensitivity than viral culture or PCR and is not recommended.

Type-Specific Serologic Tests

HSV serologic tests detect type-specific antibodies to HSV; these antibodies develop during the first several weeks following infection and persist indefinitely. Type-specific serologic tests are based on antigens specific for HSV-1 (gG1) and HSV-2 (gG2). When ordering an HSV serologic test, the clinician should request a type-specific IgG-based assay since older assays do not accurately distinguish HSV-1 from HSV-2 antibody. Because almost all HSV-2 infections are sexually acquired and HSV-2 only rarely causes oral disease, the presence of type-specific HSV-2 antibody nearly always indicates anogenital infection. In contrast, the
presence of HSV-1 antibody does not distinguish anogenital from orolabial infection. Multiple laboratory-based assays and point-of-care tests are FDA approved for the diagnosis of HSV infection. These assays detect antibodies to HSV-1, HSV-2, or both from capillary blood or serum. The sensitivities of these tests for detection of HSV-2 antibody vary from 80% to 98% and specificities of these assays are greater than 90%.\cite{93,94,95} False-negative results may occur, especially early in infection since HSV-specific antibodies can take from 2 weeks to 3 months to develop.\cite{96} False-positive results can also occur, especially in patients with low likelihood of HSV infection. Therefore, repeat or confirmatory testing (e.g., an immunoblot assay or point-of-care membrane test) may be indicated in some settings.\cite{97,98} Use of HSV IgM antibody assays is not useful for the diagnosis of genital lesions or neonatal herpes since a positive IgM test does not necessarily indicate primary infection.

**Indication for Type-specific HSV Serologic Assays**

The use of HSV type-specific serologic assays might be useful in the following scenarios:

- Recurrent or atypical genital symptoms with negative HSV cultures
- A clinical diagnosis of genital herpes without laboratory confirmation
- A sex partner with genital herpes
- As part of a comprehensive evaluation for STDs in persons with multiple sex partners, persons with HIV infection, and men who have sex with men (MSM) at increased risk for HIV acquisition

**Interpretation of HerpeSelect Assays**

The most commonly used test, HerpeSelect HSV-2 ELISA, provides a result with an index value, with values greater than 1.0 considered positive by the manufacturer. However, low index values in the range 1.1 to 3.5 may indicate false positive results, particularly in persons with HSV-1 infection. It is therefore recommended to confirm HerpeSelect ELISA index values less than 3.5 with a second test, such as the Fisher SureVue (formerly Biokit) or the gold standard University of Washington Western Blot.\cite{49}
Screening for Infection

Screening for HSV-1 or HSV-2 infections in asymptomatic persons with type-specific serologic testing is not recommended for the general population.[49,99,100,101] In December 2016, the U.S. Preventive Services Task Force recommended against routine serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant, with a grade D recommendation.[101]

Nonetheless, screening with type-specific HSV antibody should be made available to individuals who (a) request it and have risk factors for infection, (b) have a partner with genital herpes, (c) have recurrent or atypical genital symptoms or (d) have multiple sex partners. Type-specific HSV serologic tests can be considered in persons presenting for an STD evaluation, persons with HIV infection, and MSM who are at increased risk for HIV acquisition.[49,102,103]
Treatment

Oral antiviral therapy offers clinical benefits to most patients with symptomatic herpes and is the mainstay of treatment. Antiviral therapy partially controls symptoms of genital herpes when used to treat first clinical and recurrent episodes ("episodic therapy"), or when used daily to prevent recurrences or transmission ("suppressive therapy"). Antiviral therapy does not eradicate HSV, nor does it impact the risk, frequency, or severity of recurrences after the medication is discontinued. Topical antiviral treatment is discouraged from clinical use since it offers less benefit than oral therapies.[49,104,105]

Antiviral Agents Used to Treat HSV

HSV antiviral therapy includes three preferred nucleoside analogues oral medications: acyclovir, valacyclovir, and famciclovir. The anti-herpes nucleoside analogues require triphosphorylation to inhibit HSV (Figure 14).[106,107,108] The initial phosphorylation step occurs inside HSV-infected cells by virally-encoded thymidine kinase; two additional phosphate groups are added by cellular kinases, and the triphosphorylated nucleotide exerts antiviral activity by selectively inhibiting HSV DNA polymerase.[109]

First Clinical Episode

Antiviral therapy may have a dramatic impact on the first clinical episode of HSV, especially if symptoms are of less than 7 days duration at the time of initiation of therapy. Most patients with first clinical episode genital herpes infection should receive a 7 to 10 day course with an antiviral medication that has been shown to shorten the duration of viral shedding, improve symptoms, and accelerate healing (Table 1).[49,110,111,112] Therapy should be empirically started if genital herpes is suspected, rather than awaiting confirmatory laboratory results. Treatment may be extended if healing is incomplete after 10 days of therapy. Despite some evidence from animal models that early treatment may impact the long-term natural history of the infection, human trials have shown that oral acyclovir treatment of primary genital herpes does not influence the frequency of subsequent genital recurrences.[110,113,114]

Recurrent Episodes

Most patients with symptomatic genital HSV-2 infection experience recurrent outbreaks. Antiviral therapy for recurrent genital herpes can be administered either episodically (to ameliorate or shorten the duration of lesions) or continuously as suppressive therapy (to reduce the frequency of occurrences).[49] Treatment options should be discussed with all patients.

Episodic Therapy for Recurrent Genital Herpes

Successful episodic treatment requires initiation of therapy as soon as prodromal symptoms present or within one day of lesion onset. Clinicians should provide the patient with appropriate medication or a prescription and instructions to self-initiate treatment immediately when symptoms begin. Acyclovir, famciclovir, and valacyclovir are effective for episodic treatment of genital herpes, and clinical trials have established efficacy with several dosing options (Table 2).[77,111,115,116,117,118]

Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy with either acyclovir,[119,120,121] valacyclovir,[46,122,123,124] or famciclovir[46,125,126] delays the time to first genital herpes recurrence and reduces the frequency of recurrences by approximately 70% to 85%. Quality of life often is improved for patients with frequent recurrences who receive suppressive therapy when compared with episodic therapy, and the majority of patients with frequent recurrences prefer suppressive therapy (Table 3).[122,127] Two meta-analyses of HSV treatment did not demonstrate superiority of one antiviral medication over another.[128,129] Persons with 10 or more recurrences per year may benefit from increased doses of valacyclovir (1 gram daily) to suppress
Among HSV-2 discordant, HIV-seronegative heterosexual couples, when suppressive therapy with valacyclovir 500 mg daily is taken by the HSV-2 positive partner, the risk of HSV-2 transmission to the HSV-2 seronegative partner is decreased by 48%.[130] Ease of administration and cost are important considerations for suppressive treatment. For HSV discordant couples, use of suppressive antiviral therapy should be considered as part of an overall strategy to prevent HSV transmission—a strategy that includes consistent condom use, disclosure of HSV status, and avoidance of sexual activity during HSV recurrences. There is no evidence that long-term suppressive therapy in immunocompetent patients leads to antiviral resistance.[131] The frequency of recurrences may diminish over time in many patients, and a patient’s risk of transmission to partners may change over time. Therefore, clinicians should periodically reassess the need for continued suppressive therapy. It is likely that most patients who stop suppressive therapy will continue to have recurrences.

Severe Disease

Intravenous (IV) acyclovir should be provided for patients with severe HSV disease or complications requiring hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or complications of the central nervous system (e.g., meningitis or encephalitis).[49] The recommended regimen is acyclovir 5 to 10 mg/kg intravenously every eight hours for 2 to 7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy. Treatment of HSV encephalitis requires 21 days of intravenous therapy. Acyclovir dose adjustment is recommended for patients with impaired renal function.

Genital HSV in Persons with HIV Infection

Antiviral therapy has been found to be safe and effective for episodic and suppressive therapy of genital herpes in persons with HIV infection.[49,70,132,133,134] Since individuals with HIV often have more severe, prolonged cases of orolabial, genital, and perianal HSV infections compared to those without HIV infection, the recommended episodic therapy options for persons with HIV infection consists of the same antiviral medications but in higher doses and longer courses than used in persons without HIV infection (Table 4).[49,75] In persons with HIV infection, suppressive therapy with acyclovir, valacyclovir, or famciclovir is effective in decreasing HSV outbreaks (Table 5).[133,134,135] However, unlike in HSV-2 serodiscordant couples without HIV, in whom antiviral treatment significantly reduces HSV-2 transmission to the susceptible partner, treatment of HIV-1 and HSV-2 coinfection individuals with daily suppressive antiviral therapy does not reduce the transmission of HSV-2 to susceptible partners.[136] Given the increased risk of HSV shedding and genital ulcers in those who start antiretroviral therapy with a CD4 count less than 250 cells/mm$^3$, suppressive therapy may be considered to prevent immune reconstitution inflammatory syndrome (IRIS).

Antiviral-Resistant HSV

Development of acyclovir-resistant HSV is very rare among immunocompetent patients, even those who take long-term HSV suppressive therapy.[76] Most cases of acyclovir-resistant HSV have involved severely immunocompromised individuals.[74] Acyclovir resistant HSV most often results from absent or decreased production of viral thymidine kinase (TK-negative mutants) (Figure 15).[74,109] The oral antiviral agents used to treat genital HSV—acyclovir, famciclovir, and valacyclovir—all require initial activation by HSV thymidine kinase and thus provide ineffective therapy against HSV strains that have absent or decreased thymidine kinase production. In addition, the antiviral medications ganciclovir and valganciclovir are also ineffective because they require activation via a similar viral kinase. Foscarnet bypasses the thymidine kinase cascade and works by directly inhibiting the viral DNA polymerase; foscarnet is highly effective but can cause serious adverse effects.[137,138] Cidofovir does not require activation by viral thymidine kinase and both intravenous and topical forms of this drug have been successfully used to treat acyclovir-resistant HSV in a small number of immunocompromised patients.[139,140,141,142] Caution should be exerted when using intravenous cidofovir as this medication can cause severe nephrotoxicity. Topical imiquimod has been effective in persons with HIV infection who have acyclovir- and foscarnet-resistant HSV-2 infections, but
experience is limited.\textsuperscript{[143,144]} The following list are the major options used to treat acyclovir-resistant genital HSV, but management should involve consultation with an infectious diseases specialist.

- **Foscarnet**: 40 mg/kg IV every 8 to 12 hours for 21 to 28 days or until clinical resolution is attained. Foscarnet can potentially cause severe adverse effects, including nephrotoxicity and electrolyte disturbances.
- **Cidofovir**: 5 mg/kg IV once weekly for 21 to 28 days or until clinical resolution is attained. Note the cidofovir can cause severe renal abnormalities.
- **Imiquimod 5% cream**: Apply to lesions three times per week for 21 to 28 days.
- **Cidofovir 1% gel**: Apply to lesions three times per week for 21 to 28 days, or longer based on the clinical response. This preparation is not commercially available and must be compounded by a pharmacist.
Genital HSV in Pregnancy and Preventing Neonatal Infection

Risk of Neonatal Herpes Infection

Neonatal HSV infection is defined as HSV infection that develops in a newborn during the first 28 days after birth.[145] Although neonatal HSV occurs infrequently, the incidence (1 in 3,200 deliveries) is higher than with other congenital infections, including syphilis, toxoplasmosis, and rubella.[86,145] Approximately 85% of neonatal HSV infections result from intrapartum (perinatal) infection, with the remaining cases involving HSV exposure and transmission during the intrauterine (in utero) or postpartum (postnatal) periods.[146] The risk of intrapartum HSV transmission is significantly higher among women who newly acquire genital HSV-2 (or HSV-1) during pregnancy than women who have reactivation of genital HSV during pregnancy.[145] The highest HSV transmission risk occurs when the pregnant woman acquires HSV is acquired near the time of delivery.[85,86,147,148,149] If a pregnant woman has primary genital HSV infections and is shedding HSV at the time of delivery, the risk of HSV transmission to the neonate is 10 to 30 times higher than if she is shedding HSV during a recurrent HSV infection.[146] When a mother has genital HSV infection, the following five factors have been identified as the major influence for risk of transmission:[146]

- Whether the HSV infection is primary or recurrent
- HSV antibody status of the mother
- Duration of membrane rupture
- Integrity of mucocutaneous barrier
- Mode of the delivery (vaginal versus cesarean)

General Approach to Preventing Neonatal HSV Infection

Strategies used to prevent neonatal herpes depend on preventing acquisition of genital HSV infection in susceptible women during late pregnancy and avoiding exposure of the neonate to maternal herpetic lesions and viral shedding during birth.[49] All pregnant women should be questioned about a history of genital HSV, but routine type-specific HSV antibody screening of pregnant women is not recommended.[49,150] At the time women present in labor, the clinician should carefully ask the woman whether she has any active genital lesions or prodromal genital symptoms consistent with herpes.[49] It is important that optimal prevention measures are utilized to prevent HSV transmission and development of neonatal HSV disease. The following will address six major scenarios and issues related to preventing neonatal HSV transmission and neonatal disease:

- Indications for cesarean section
- Approach to women with no history of genital herpes
- Approach to women with a history of recurrent HSV and no active lesions
- Approach to women with active genital HSV lesions at the time of labor
- Evaluation and management of an infant exposed to HSV
- Management of a neonates infected with HSV

Indications for Cesarean Section

The American Academy of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend performing a cesarean section for any pregnant woman with active HSV genital lesions or prodromal symptoms at the time of labor; ideally the cesarean section should be performed before rupture of membranes.[146,150] The recommendation to perform cesarean section in this setting should be followed regardless of whether the HSV lesions are a result of recent HSV acquisition or reactivation of established HSV infection.[49,55] In addition, use of invasive monitors during labor should be limited.[49,86] Delivery by cesarean section does not completely eliminate the risk for HSV transmission to the infant.[150,151] Pregnant women with a history of recurrent HSV, but no symptoms or signs of genital herpes or prodromal symptoms, can give birth vaginally, regardless of whether they are taking prophylactic suppressive antiviral therapy.
Women with No History of Genital HSV

For pregnant women without a history of genital HSV, routine HSV-2 serologic screening is not recommended. Since pregnant women who acquire genital herpes near the time of delivery have a high risk for transmission of HSV to the neonate, all pregnant women without a history of genital HSV should receive counseling to abstain from vaginal intercourse during the third trimester of pregnancy with any sexual partner known or thought to have genital herpes. Similarly, if the woman does not have a history of ever having orolabial HSV, they should also abstain from receptive oral sex (cunnilingus) with any partner who has known or suspected orolabial herpes. The STD Treatment Guidelines do not recommend using suppressive antiviral therapy for HSV-seropositive women with no history of genital HSV.

Asymptomatic Women with a History of Recurrent Genital HSV

Prophylactic suppressive therapy with acyclovir or valacyclovir beginning at 36 weeks gestation should be offered to all women with a history of genital herpes since it has been shown to reduce the risk of HSV recurrence at delivery by 75%, the risk of cesarean delivery for recurrent genital herpes by 40%, and the risk of HSV shedding at delivery. The dose of suppressive therapy is higher in pregnant women due to enhanced renal excretion of the antiviral medications. Use of suppressive therapy, however, does not completely eliminate HSV detection late in pregnancy and cases of neonatal HSV transmission have occurred despite maternal prenatal antiviral suppressive therapy. Suppressive treatment can be stopped after delivery. Studies of pregnancy outcomes following prenatal acyclovir exposure have not identified an increased risk of birth defects compared with the general population. 

Women with Active Genital Herpes Lesions Near or at Delivery

Women can have active HSV lesions at the time of delivery either through acquisition of HSV infection near delivery or reactivation of established HSV infection. The American Academy of Obstetricians and Gynecologists recommends cesarean section (ideally, before rupture of membranes) for any pregnant woman with active genital lesions or prodromal symptoms at the time of delivery. In addition, use of invasive monitors during delivery should be limited. Delivery by cesarean section does not completely eliminate the risk for HSV transmission to the infant. Most expert recommend that women with first episode genital HSV infection near term should be managed in consultation with maternal-fetal medicine and infectious-disease specialists. The initial management should include prompt antiviral treatment of the genital HSV infection.

Management of Neonatal Herpes

Infants with HSV disease should be treated with parenteral acyclovir therapy in consultation with a pediatric infectious disease specialist. Treatment duration is generally 14 days for SEM disease or 21 days for disseminated and CNS disease, and suppressive therapy after CNS disease may be indicated for up to 6 months; detailed guidelines are available for management of neonates who are delivered vaginally in the presence of maternal genital HSV lesions. Despite improvement in patient outcomes with parenteral acyclovir and subsequent suppressive oral acyclovir therapy, neurodevelopmental outcomes remain poor in neonates with CNS disease at birth.

Genital HSV Counseling in Pregnancy:

- Ask all pregnant women whether they have a history of genital herpes;
- Counsel all women without known genital herpes to avoid intercourse during the third trimester with partners known or suspected to have genital herpes;
- Counsel all women without known orolabial herpes to avoid receptive oral sex (cunnilingus) during the third trimester with partners known or suspected to have orolabial herpes; and
- At the onset of labor, question all women about symptoms of genital herpes, (including prodromal symptoms) and examine all women for herpetic lesions.
Prevention

Given that HSV-2 is the most common cause of genital ulcer disease in the United States and globally, and that HSV-2 increases the risk of acquiring and transmitting HIV infection, effective prevention strategies are essential in reducing the global burden of genital herpes.

Proven Strategies to Prevent HSV Transmission

Multiple strategies, including suppressive antiviral therapy, consistent use of condoms, and disclosure of HSV status to partners, have been shown to reduce HSV transmission. High efficacy in preventing HSV transmission is most likely achieved when a combination of these methods are used.

Suppressive Antiviral Therapy

Studies have shown that daily therapy with either acyclovir, famciclovir, or valacyclovir significantly reduces subclinical shedding of HSV-2.[46,130,157,158,159,160,161] Daily suppressive therapy with valacyclovir can reduce the risk of transmission in heterosexual discordant partnerships shown in a large, randomized trial that enrolled 1484 HIV-seronegative, heterosexual HSV-2 discordant sexual partners and found that acquisition of HSV-2 occurred in 1.9% of persons whose partners received suppressive valacyclovir (500 mg daily) compared to 3.6% of those randomized to placebo (48% reduction). (Figure 17).[130] In this study, couples were also counseled about safer sex/condom use and about the signs of genital herpes.[130] In contrast, in a later study that involved persons with HSV-2 and HIV-1 coinfection living in sub-Saharan Africa, suppressive therapy with acyclovir 400 mg twice daily did not prevent transmission of HSV-2 to susceptible heterosexual partners.[136] Taken together, these studies suggest suppressive antiviral therapy is effective for preventing transmission of HSV-2 among HIV-seronegative, but may not be as effective in HIV-seropositive persons. In addition available data suggest that famciclovir is less effective than valacyclovir in reducing HSV shedding.[46] The use of suppressive antiviral therapy to prevent genital HSV-1 transmission has not been studied.

Condoms

Several studies have examined the efficacy of condoms to prevent HSV-2 transmission.[41,162] In a pooled analysis of 6 prospective studies, consistent use of condoms reduced the risk of HSV-2 transmission by 30%.[163] The risk of HSV-2 acquisition was estimated to decrease by 7% for every 25% increase in the frequency of condom use, suggesting that even inconsistent condom use can provide some protection. In another study that compared the risk of HSV-2 acquisition in individuals during self-reported sexual acts with and without condom use, there was a 3.6% increase in odds of HSV-2 acquisition per unprotected sexual act.[164] Therefore, available data suggest condoms can play a significant role in the overall strategy for preventing HSV acquisition and transmission, but it is important to note the impact is only modest. This relatively low efficacy of condoms in preventing HSV transmission is likely explained by anatomical areas of HSV shedding and exposure that are not protected by a condom.

Disclosure of HSV-2 Serostatus

The disclosure of HSV-2 infection also appears to reduce the risk of HSV transmission between HSV-discordant partners.[165] In a study that enrolled 199 persons who acquired genital herpes, the median time of HSV-2 acquisition was significantly delayed among persons whose partners had disclosed that they had HSV-2 as compared to those who did not disclose (270 versus 60 days). Disclosure of genital HSV-1 infection may also delay the time to HSV-1 acquisition, although further studies are needed.[165]

Male Circumcision

Male circumcision is an underutilized strategy for the prevention of sexually transmitted infections in men and their female sexual partners. Male circumcision significantly reduces the incidence of HSV-2 infection in HIV-
uninfected men: in two independent randomized trials of male circumcision in Rakai, Uganda, male circumcision was found to reduce HSV-2 seroconversion by 25%.\cite{166,167} In addition, male circumcision has been shown to reduce heterosexual acquisition of HIV, human papilloma virus (HPV), and genital ulcer disease among men as well as HPV, genital ulcer disease, bacterial vaginosis, and trichomoniasis among female partners \cite{168}.

Investigational Strategies to Prevent HSV Transmission

HSV Vaccines

Although there are no currently available vaccines for HSV infection, several vaccines are currently in various stages of development, including preventative vaccines aimed at reducing the risk of HSV-2 acquisition for HSV-2 seronegative persons and therapeutic vaccines to reduce the risk of recurrent disease and transmission for HSV-2 seropositive persons.\cite{30,169,170}

Tenofovir Disoproxil Fumarate Preexposure Prophylaxis (PrEP)

Tenofovir disoproxil fumarate (DF) is a nucleotide analog reverse transcriptase inhibitor frequently used as a component of antiretroviral therapy for persons with established HIV infection and in the fixed-dose combination with emtricitabine (tenofovir DF-emtricitabine) as preexposure prophylaxis (PrEP) prevention medication for HIV seronegative individuals at risk of acquiring HIV.\cite{68,171,172,173,174,175} The potential for tenofovir DF to reduce HSV-2 acquisition was identified in one of the HIV PrEP studies, CAPRISA 004, in which pericoital application of tenofovir 1% vaginal gel reduced HSV-2 acquisition in women (incidence rate was 10.2 cases per 100 person-years in tenofovir gel group compared with 21.0 cases per 100 person-years in placebo group).\cite{68,176} This result was reaffirmed in the VOICE trial, in which women who regularly used tenofovir gel were 46% less likely to acquire HSV-2 compared to women who seldom or never used the gel.\cite{177} The use of oral tenofovir DF or co-formulated tenofovir DF-emtricitabine for PrEP was also associated with decreased acquisition of HSV-2 among heterosexual HIV-1 uninfected men and women in Africa.\cite{178} Among HSV-2 seropositive women, however, neither oral tenofovir nor tenofovir gel significantly reduced HSV-2 shedding or lesion rate.\cite{179} Although these studies are promising, insufficient data exist to recommend the use of tenofovir gel or oral tenofovir DF for the prevention of HSV. Further, these agents are not FDA-approved for the prevention of HSV.
Patient Counseling and Education

Counseling plays an integral role in the clinical management of a patient diagnosed with genital herpes and the counseling should include, when applicable, a discussion of the natural history of genital herpes, sexual and perinatal transmission, and methods to reduce transmission to others. Although initial counseling can be provided at first visit, many patients benefit from learning about the chronic aspects of the disease after the acute illness subsides. Numerous resources are available to assist patients and clinicians in counseling (see Patient Resources below). Persons with genital herpes may experience anxiety concerning genital herpes that does not reflect the actual clinical severity of their disease; there is significant morbidity attributed to the psychological burden of HSV related to the need for behavior change and for disclosure to sexual partners. Counseling has two main goals: (a) to help patients better understand and cope with chronic HSV infection, and (b) to prevent sexual and perinatal HSV transmission. When counseling persons with genital HSV infection, issues related to the nature of the disease, transmission, and risk reduction should be addressed.

Nature of the Disease

- HSV-2 is the most common cause of recurrent genital herpes.
- Asymptomatic infection is common, and more than 85% of persons infected with HSV-2 have not been diagnosed.
- The clinical manifestations of herpes infection vary significantly in patients with first clinical episode or recurrent infection.
- Recurrent disease is common and is precipitated by multiple known factors (trauma, fever, ultraviolet light, physical or emotional stress, immunosuppression, fatigue, menses, sexual intercourse) as well as unknown factors.
- Neonatal HSV disease is rare, and the risk is highest among women who develop primary HSV infection at or near the time of delivery.
- Persons with suspected or confirmed primary genital HSV infection should be treated with antiviral therapy.
- The use of episodic therapy may shorten the duration of recurrent episodes, and suppressive therapy may reduce the frequency of symptomatic disease (“outbreaks”).
- Persons infected with genital HSV should disclose their HSV status to current and future sexual partners.

Transmission Issues

- Sexual transmission of HSV-1 and HSV-2 can occur through genital-to-genital, oral-to-genital, or genital-to-oral contact.
- The efficiency of sexual transmission is thought to be greater from men to women than from women to men.
- HSV can be transmitted perinatally at the time of delivery through direct mucosal or skin contact.
- Persons who are asymptomatic or unaware of their genital infection are responsible for transmitting the majority of genital HSV infections.
- The most common sites of asymptomatic shedding are the vulva and perianal areas in women and penile skin and perianal area in men.
- The rate of asymptomatic shedding is highest in the first year after infection.
- Antiviral suppressive therapy dramatically reduces HSV-2 shedding by about 70% to 80%, but does not eradicate it.

Risk Reduction

- Persons with HSV-2 infection should abstain from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
- Male latex condoms, when used consistently and correctly, can reduce (but not eliminate) the risk for
genital herpes transmission.

- Daily valacyclovir has been shown to decrease the rate of HSV-2 transmission in HSV-2 discordant, HIV-seronegative heterosexual couples.
- Tenofovir DF has been shown to reduce the risk of HSV-2 acquisition in heterosexual couples and reduce the frequency of symptomatic disease in men who have sex with men, but is not FDA-approved for prevention of HSV infection.
- Male circumcision reduced HSV-2 seroconversion by 25% in randomized clinical trials in sub-Saharan Africa.

Counseling Antibody-Positive Asymptomatic Persons

Asymptomatic persons who receive a diagnosis of HSV-2 infection by type-specific serologic testing should receive the same counseling messages as persons with symptomatic infection. In addition, such persons should be educated about the clinical manifestations of genital herpes. The psychological effects of a serologic diagnosis of HSV-2 infection in persons with asymptomatic or unrecognized genital herpes appear to be transient.\(^{[180, 181, 182]}\) Pregnant women and women of childbearing age who have genital herpes should inform the providers who care for them during pregnancy and those who will care for their newborn infant about their infection.

Patient Resources

- Herpes-American Sexual Health Association
- University of Washington Virology Research Clinic
- Centers for Disease Control and Prevention—Genital Herpes
Summary Points

- Genital herpes is the leading cause of genital ulcer disease worldwide and one of the most prevalent sexually transmitted infections in the United States, though there are significant racial and gender disparities in seroprevalence rates, with the highest rates among black women.
- Genital herpes is a chronic viral infection caused by HSV-2, or less commonly, HSV-1, and is characterized by periods of latency punctuated by periods of viral shedding.
- More than 85% of persons infected with genital herpes are unaware of their infection, and asymptomatic shedding of HSV in these persons accounts for the majority of transmitted genital HSV infections.
- Complications of genital herpes infections include aseptic meningitis, transverse myelitis, autonomic dysfunction, fulminant hepatitis, neonatal herpes, and both acquisition and transmission of HIV infection.
- Screening for genital herpes is not recommended for the general population, but when testing is indicated, virologic testing (with polymerase chain reaction, or PCR) or viral culture is generally preferred to serologic testing.
- Antiviral therapy with acyclovir, valacyclovir, or famciclovir can be used to treat symptoms ("episodic therapy") and to prevent recurrences and reduce viral shedding and transmission ("suppressive therapy").
- Prophylactic therapy with acyclovir or valacyclovir beginning at 36 weeks gestation should be offered to all women with a history of genital herpes since it has been shown to reduce the risk of HSV recurrence at delivery by 75%, the risk of cesarean delivery for recurrent genital herpes by 40%, and the risk of HSV shedding at delivery.
- Counseling plays an integral role in the management of a patient diagnosed with HSV infection given the significant morbidity attributed to the psychological burden of HSV related to the need for behavior change and for disclosure to sexual partners.
Citations


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References


Figures

Figure 1 Genital Herpes—Initial Visits to Physicians’ Offices, United States, 1966-2014

NOTE: These data are from the National Disease and Therapeutic Index, IMS Health, Integrated Promotional Services™. IMS Health Report, 1966-2014. The 2015 data were not available to include in the report. The relative standard errors for genital HSV infection estimates of more than 100,000 range from 18% to 23%.

Figure 2 HSV-2 Seroprevalence by Sex and race, NHANES 2007-2010

This figure is based on HSV-2 seroprevalence data from persons aged 14 to 49 years of age in the National Health and Nutrition Examination Survey (NHANES) conducted 2007-2010. For both males and females, the HSV-2 seroprevalence is much higher in non-Hispanic blacks than non-Hispanic whites.

Figure 3 HSV-2, Black to White Prevalence Ratios, NHANES 1988-2010

This figure is based on HSV-2 seroprevalence data from persons aged 14 to 49 years of age in the National Health and Nutrition Examination Surveys (NHANES); the data shown is for the time periods 1988 to 1994, 1999 to 2002, 2003 to 2006, and 2007 to 2010.

Figure 4 Herpes simplex Virus—Transmission Electron Microscopic

This negatively-stained transmission electron microscopic (TEM) image revealed the presence of numerous herpes simplex virions. At the core of its icosahedral proteinaceous capsid, the HSV contains a double-stranded DNA linear genome.

Source: Centers for Disease Control and Prevention Public Health Image Library. Dr. Fred Murphy & Sylvia Whitfield, 1975.
**Figure 5 Basic Structure of Herpes Simplex Virus**

Herpes simplex virus is approximately 150 to 200 nm diameter. The basic structural features for HSV-1 and HSV-2 are the same. The image on left depicts intact virion and image on right shows cross-sectional view.

Illustration by Jared Travnicek, Cognition Studio
**Figure 6 Duration of Genital HSV-2 Shedding per Episode**

This graphic shows the duration of genital HSV-2 shedding per episode for 72 episodes. As shown, approximately 60% of the episodes were less than 24 hours in duration. The median duration of shedding was 13 hours.

Figure 7 Primary Genital HSV Infection

This photograph shows characteristic findings consistent with primary genital HSV infection. These findings include bilateral involvement and extensive number of lesions.

Source: University of Washington Virology Research Clinic
Figure 8 Clinical and Virologic Course of Genital HSV in Primary Infection

Note: the height of the curves correlates with the general severity of symptoms.

**Figure 9 Recurrent Genital HSV Lesions—Vesicle Phase**

This patient with recurrent HSV has a crop of lesions at the early vesicular stage on the shaft of the penis.

Source: University of Washington Virology Research Clinic
Figure 10 Recurrent Genital HSV—Wet Ulcer Phase

Left labial ulcerative lesion in woman with recurrent HSV.

Source: University of Washington Virology Research Clinic
Figure 11 Recurrent Genital HSV Lesion—Dry Crusting Phase

This patient with recurrent herpes presented with a several day history of irritation on the shaft of the penis followed by itching, burning, and the appearance of a small ulcerative lesion (black arrow) just below the glans. In a sample taken from the ulcer, HSV was detected by PCR. At the time the patient presented for evaluation, the HSV lesion was in the dry crusting phase.

Source: University of Washington Virology Research Clinic
Figure 12 (Image Series) - Recurrent HSV in Gluteal Cleft (Image Series) - Figure 12 (Image Series) - Recurrent HSV in Gluteal Cleft

Image 12A: Pustule Phase

This patient has longstanding recurrent genital HSV-2. She noted onset of pruritus in gluteal cleft region 2 days prior to presentation. This image shows a cluster of lesions in pustule phase in the gluteal cleft.

Source: University of Washington Virology Research Clinic
Figure 12 (Image Series) - Recurrent HSV in Gluteal Cleft
Image 12B: Dry Crusted Phase

This photograph shows healing cluster HSV lesions in gluteal cleft; these lesions progressed to the dry crust phase after approximately 5 days.

Source: University of Washington Virology Research Clinic
**Figure 13 Recurrent Genital HSV with Subtle Lesion**

This photograph shows subtle HSV lesion that lesions may develop as minimally symptomatic or asymptomatic fissures or linear lesions.

Source: University of Washington Virology Research Clinic
**Figure 14 Acyclovir Mechanism of Action**

As acyclovir enters cells infected with HSV, it is initially activated by the viral thymidine kinase (TK); the second and third phosphorylation steps occur through cellular kinases. The active drug acyclovir triphosphate then inhibits HSV DNA replication.

Illustration by David H. Spach, MD
**Figure 15 Acyclovir-Resistant HSV**

Most acyclovir-resistant HSV occurs via the mechanism of decreased or absent production of thymidine kinase (TK) by HSV. The strains are referred to as HSV TK- mutants. With inadequate production of TK, acyclovir does not undergo the mandatory initial phosphorylation step and HSV replication proceeds uninhibited.

Illustration by David H. Spach, MD
Figure 16 Primary Oral HSV Infection

This photograph shows characteristic finds with primary oral HSV—bilateral involvement and large number of lesions.

Source: University of Washington Virology Research Clinic
This study involved 1484 HSV-serodiscordant, heterosexual, monogamous couples. Partners with symptomatic genital HSV-2 infection were randomized to receive 8 months of oral valacyclovir 500 mg once daily or placebo.

Table 1. 2015 STD Treatment Guidelines: Genital Herpes
Treatment of First Clinical Episode of Genital Herpes

<table>
<thead>
<tr>
<th>Recommended for Treatment of First Clinical Episode of Genital Herpes</th>
<th>Acyclovir</th>
<th>400 mg orally three times a day for 7-10 days</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Note:</td>
<td>Treatment can be extended if healing is incomplete after 10 days of therapy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment of First Clinical Episode of Genital Herpes</th>
<th>Acyclovir</th>
<th>200 mg orally five times a day for 7-10 days</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Note:</td>
<td>Treatment can be extended if healing is incomplete after 10 days of therapy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment of First Clinical Episode of Genital Herpes</th>
<th>Valacyclovir</th>
<th>1 g orally twice a day for 7-10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Note:</td>
<td>Treatment can be extended if healing is incomplete after 10 days of therapy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment of First Clinical Episode of Genital Herpes</th>
<th>Famciclovir</th>
<th>250 mg orally three times a day for 7-10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Note:</td>
<td>Treatment can be extended if healing is incomplete after 10 days of therapy.</td>
</tr>
</tbody>
</table>

### Table 2. 2015 STD Treatment Guidelines: Genital Herpes

**Episodic Therapy for Recurrent Genital Herpes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>400 mg orally three times a day for 5 days</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>800 mg orally twice a day for 5 days</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>800 mg orally three times a day for 2 days</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>500 mg orally twice a day for 3 days</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1 g orally once a day for 5 days</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>125 mg orally twice daily for 5 days</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>1 g orally twice daily for 1 day</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500 mg orally once, followed by 250 mg orally twice daily for 2 days</td>
</tr>
</tbody>
</table>

### Table 3. 2015 STD Treatment Guidelines: Genital Herpes

**Suppressive Therapy for Recurrent Genital Herpes**

The frequency of genital herpes recurrences diminishes over time in many persons, potentially resulting in psychological adjustment to the disease. Therefore, periodically during suppressive treatment (e.g., once a year), providers should discuss the need to continue therapy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acyclovir</strong></td>
<td>400 mg orally twice a day</td>
</tr>
<tr>
<td><strong>Valacyclovir</strong></td>
<td>500 mg orally once a day</td>
</tr>
<tr>
<td><strong>Famciclovir</strong></td>
<td>250 mg orally twice a day</td>
</tr>
</tbody>
</table>

Note: Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in persons who have very frequent recurrences (i.e., ≥10 episodes per year).

### Table 4. 2015 STD Treatment Guidelines: Genital Herpes

**Episodic Therapy for Recurrent Genital Herpes in Persons with HIV**

<table>
<thead>
<tr>
<th>Recommended for Episodic Therapy for Recurrent Genital Herpes in Persons with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acyclovir</strong></td>
</tr>
<tr>
<td>400 mg orally three times a day for 5-10 days</td>
</tr>
<tr>
<td><strong>Valacyclovir</strong></td>
</tr>
<tr>
<td>1 g orally twice a day for 5-10 days</td>
</tr>
<tr>
<td><strong>Famciclovir</strong></td>
</tr>
<tr>
<td>500 mg orally twice a day for 5-10 days</td>
</tr>
</tbody>
</table>

For severe HSV disease, initiating therapy with acyclovir 5-10 mg/kg IV every 8 hours might be necessary.

### Table 5. 2015 STD Treatment Guidelines: Genital Herpes
Suppressive Therapy in Persons with HIV

<table>
<thead>
<tr>
<th>Recommended for Suppressive Therapy in Persons with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acyclovir</strong></td>
</tr>
<tr>
<td>400–800 mg orally twice to three times a day</td>
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</table>

<table>
<thead>
<tr>
<th>Recommended for Suppressive Therapy in Persons with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valacyclovir</strong></td>
</tr>
<tr>
<td>500 mg orally twice a day</td>
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</table>

<table>
<thead>
<tr>
<th>Recommended for Suppressive Therapy in Persons with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Famciclovir</strong></td>
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<tr>
<td>500 mg orally twice a day</td>
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Table 6. 2015 STD Treatment Guidelines: Genital Herpes
Suppressive Therapy of Pregnant Women with Recurrent Genital Herpes

<table>
<thead>
<tr>
<th>Recommended for Suppressive Therapy of Pregnant Women with Recurrent Genital Herpes</th>
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<tbody>
<tr>
<td><strong>Acyclovir</strong></td>
</tr>
<tr>
<td>400 mg orally three times a day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Suppressive Therapy of Pregnant Women with Recurrent Genital Herpes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valacyclovir</strong></td>
</tr>
<tr>
<td>500 mg orally twice a day</td>
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