Genital Herpes

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Module 2: Self-Study Lessons
Lesson 5: Genital Herpes

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Introduction

Genital herpes is the leading cause of genital ulcer disease worldwide. Genital herpes is caused by herpes simplex virus (HSV) (Figure 1), including type 2 (HSV-2) and type 1 (HSV-1). Clinical episodes of genital herpes are categorized as first-episode primary, nonprimary infection, or recurrent symptomatic infection. Asymptomatic infection is common, and persons with asymptomatic or unrecognized genital herpes account for a substantial proportion of genital HSV infections. Transmission of HSV can occur from mothers with genital herpes to their neonates, especially in mothers who have a primary genital HSV infection in the third trimester of pregnancy. Highly sensitive and specific polymerase chain reaction (PCR) tests are available for diagnostic purposes. Routine herpes serologic screening for the general population is not recommended, but two-step type-specific serologic screening can have value in certain situations. Oral antiviral therapy can be used as effective episodic and suppressive therapy for genital herpes. Multiple prevention strategies have been used in an effort to reduce HSV transmission and acquisition.

Epidemiology in the United States

Background and Burden of Disease

Since genital herpes is not a nationally notifiable condition, the true prevalence (persons who are living with genital herpes) and incidence (new cases of genital herpes) are difficult to accurately determine. Genital herpes is among the most prevalent sexually transmitted infections in the United States. Seroprevalence estimates for HSV-1 and HSV-2 in the United States are based on data generated by the National Health and Nutrition Examination Survey (NHANES); these data are also used to make HSV incidence estimates.[1,2] Although both HSV-1 and HSV-2 can potentially cause genital infection, HSV-2 causes most recurrent genital herpes.[2,3,4] In 2018, there were an estimated 18.6 million people 18–49 years of age living with genital herpes caused by HSV-2, plus several million additional persons living with genital herpes caused by HSV-1.[2] Overall, the burden of genital herpes in the United States is greater in women than in men, with women accounting for approximately two-thirds of all people with genital herpes.[4] Recent studies have shown, that in some populations, HSV-1 has become the leading cause of new genital herpes infections in the United States.[5,6]

Epidemiology of Genital HSV-2 Infection

In 2018 alone, approximately 572,000 persons 18–49 years of age newly acquired HSV-2 in the United States.[2] Using this 2018 incidence of HSV-2 infections, the lifetime direct medical cost for persons who acquired HSV-2 in the United States in 2018 was calculated at $91 million.[7] Based on NHANES data collected from 2015-2016, the HSV-2 seroprevalence rate for that period was 12.1% for persons 14–49 years of age.[1] The following summarizes several key features from the more detailed NHANES 2015-2016 report for HSV-2 seroprevalence for persons 14–19 years of age (Figure 2).[1]

- **Seroprevalence Trends**: There was a significant decline in the HSV-2 seroprevalence rate from 1999-2000 (18.0%) to 2015-2016 (12.1%).
- **Sex**: The HSV-2 seroprevalence was nearly 2-fold higher in females (15.9%) compared with males (8.2%).
- **Age Groups**: The HSV-2 seroprevalence increased with age, with significant continued increases in the different age groups from 14–49 years.
- **Racial/Ethnic Groups**: The HSV-2 seroprevalence rates were highest in non-Hispanic Black individuals during the time periods from 1999-2000 to 2015-2016.[Q] Epidemiology of HSV-2

Epidemiology of Genital HSV-1 Infection

First-episode genital herpes caused by HSV-1 has been identified with increased frequency among young women, college students, and men who have sex with men (MSM).[5,8,9,10,11] Acquisition of genital HSV-1 can occur through genital-genital contact or via receptive oral sex.[12,13] In the United States, HSV-1 has now replaced HSV-2 as the leading cause of first-episode genital herpes.[2,4,10] One proposed reason for this shift is decreasing HSV-1 orolabial infection in childhood and early adolescence,[11] with first exposure to HSV-1 occurring later in life with sexual activity. Changing sex practices in young adults, namely an increase in oral-genital sex, may also contribute to the changing epidemiology of genital herpes.[11] Seroprevalence data for HSV-1, such as those reported in the NHANES studies, do not provide accurate information on genital herpes infections, since it is not possible to determine whether infection is oral or genital with a positive HSV-1 serologic test alone. Nevertheless, HSV-1 does contribute significantly to the burden of genital HSV, and there are likely at least several million prevalent genital HSV-1 infections in the United States.[2] The following image series summarizes several key features from the more detailed NHANES 2015-2016 report for HSV-1 seroprevalence for persons 14–19 years of age (Figure 3).[1]

Microbiology, Pathogenesis, and Transmission

Viral Structure

Both HSV-1 and HSV-2 are 150 to 200 nm alpha-herpesviruses that are structurally comprised of four major components: DNA, nucleocapsid, tegument, and lipid envelope (Figure 4).[14,15] 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 nucleocapsid or viral core. The tegument, 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. Differences in glycoprotein G (gG) between HSV-1 and HSV-2 have been utilized in the development of HSV type-specific serologic tests.[16,17][Q] Biology of HSV Infection

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 via retrograde transport. Once this transport is completed, HSV establishes persistent infection as an episome in the nerve cell bodies in the sacral ganglia and paraspinal ganglia.[18] In the ganglia, HSV enters a latent (off) state, characterized by expression of viral microRNAs and the latency-associated transcript. These factors are important for preventing neuronal apoptosis, maintenance of latency, and regulation of spontaneous viral reactivation.[19,20,21,22] Because HSV is not cleared from neurons, the ganglia become lifelong reservoirs for the virus.

Viral Reactivation

The steps leading to the transition between latent infection and reactivation (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.[23] This early viral reactivation leads to transcription of the immediate-early (IE) viral genes; early and late viral genes are then transcribed, and proteins such as the viral protein 16 (VP16) lead to chromatin remodeling.[24,25] 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.[26,27]

Dynamics of Viral Shedding

Although HSV was previously thought to be in a latent state most of the time, shedding studies involving intensive 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 5).[28] Mathematical modeling studies suggest that latency is dynamic, with small quantities of virus released from the ganglia on most days.[29] Tissue-resident memory CD8+ T lymphocytes, which can be found in genital tissue, are thought to serve a major role in containing viral shedding.[30,31] The frequent viral shedding and primed host immune response may contribute to increased genital tract inflammation noted in persons with HSV-2 infection.[32] In addition, HSV-2 reactivation selectively recruits CD4 cells (HIV target cells) to the genital skin and mucosa, which can serve as target cells for HIV-1.[33,34,35]

Asymptomatic Viral Shedding

Studies of HSV-2 seropositive persons have documented that most have asymptomatic viral shedding.[36,37] 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.[37,38] Asymptomatic viral shedding is shorter than shedding during clinical recurrences, but the quantity of virus shed is similar in symptomatic and subclinical episodes.[36] 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.[28,39] Most HSV-2 transmission is thought to occur with viral shedding during asymptomatic shedding episodes.[40,41,42] Antiviral suppressive therapy dramatically reduces HSV-2 shedding by 70 to 80%, but it does not eradicate it.[26,43] Genital HSV-1 shedding is less frequent than HSV-2 shedding, with shedding detected by culture on 2% of days.[26,38,44,45] Following first-episode HSV-1, shedding is common but decreases significantly over a 1-year period.[46] Shedding following first-episode HSV-1 is higher in persons with primary HSV-1 infection (absent HSV antibody at baseline) compared to those with nonprimary HSV-1 infection.[46]

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, genital-to-oral, anal-to-genital, and genital-to-anal contact (Figure 6).[47] The transmission of HSV-2 most often involves asymptomatic shedding of HSV-2, often in persons unaware that they have HSV infection.[40,41,42] The relative efficiency of sexual transmission is thought to be greater from men-to-women than from women-to-men.[38] In addition, HSV can be transmitted perinatally 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, usually during primary infection.[48] [Q] Transmission of HSV-2

Clinical Manifestations

Types of Genital HSV Infection

The clinical manifestations of genital herpes vary significantly when comparing a 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.[31] Women tend to have more severe disease, characterized by more systemic symptoms when compared with men.[49,50] The incubation period between HSV acquisition and onset of symptoms is, on average, 4 days (ranging from 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.[49,51] Herpes simplex virus 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 preexisting antibodies to the other virus type), 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 (1) at the time of primary infection (absence of antibody to HSV-1 and HSV-2), (2) at the time of nonprimary infection (presence of HSV-1 or HSV-2 antibody with acquisition of the other viral type), or (3) 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.[50]

Primary Genital Infection

Primary infection is defined as the first infection with either HSV-1 or HSV-2 with the absence of antibodies to either type. Primary genital infection is often symptomatic, but patients may have an 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.[52] The following summarizes key features that may occur with primary HSV-1 or HSV-2 genital infection:

- Multiple severe 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 lesions evolving from vesicles to pustules to wet ulcers to dry crusts (Figure 8).[53]
- The median duration of viral shedding is about 10 to 12 days and correlates with the time from the onset of vesicles to the crusting of lesions.[54]
- 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 the onset of lesions and gradually recede over the next 3 to 4 days.[55]
- In women, HSV shedding from the cervix occurs in 80 to 90% of primary HSV-1 and HSV-2 infections.[50] 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.
- Common manifestations of herpes proctitis include fever, pain, discharge, tenesmus, and constipation; some individuals will have severe anal ulcerations visible on anoscopy. In addition, some will develop symptoms of autonomic dysfunction, including difficulty urinating.[56]
- Infection of the urethra and/or meatus may cause a clear mucoid discharge that may be mistaken for

chlamydial or gonococcal urethritis.[57]

[Q] Presentation of Primary HSV-2 Infection

Nonprimary Infection

The term nonprimary HSV infection most often refers to infection with HSV-1 or HSV-2 in an individual with preexisting 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.[58,59] Nonprimary infection can also occur when a person has asymptomatic HSV-2 acquisition with development of antibodies to HSV-2, followed later by a symptomatic HSV-2 outbreak.

Recurrent Symptomatic Infection

Recurrent symptomatic genital herpes refers to recurrences in the setting of a known diagnosis of genital HSV. Recurrent symptomatic genital herpes is characterized by mild, localized symptoms that typically resolve within 3 to 5 days after onset. Prodromal symptoms (localized tingling, burning) due to HSV traveling along the nerve axons are common and begin 12 to 24 hours before lesions appear. Lesions typically form as vesicles or pustules that progress to a wet ulcer, which gradually becomes dry and crusted (Figure 9). The time for lesions to heal is usually more rapid than with the initial infection. For HSV-2, the frequency of symptomatic genital herpes reactivation decreases from a median of 4 to 5 recurrences during the first year to 3 to 4 recurrences in subsequent years. For genital HSV-1, the frequency of symptomatic genital herpes is a median of 1 per year during the first year, with no outbreaks typically in subsequent years.[60] The number of subsequent episodes of symptomatic infection is higher in women than in men and in persons who experience prolonged symptoms associated with primary infection.[44,49,61]

Unrecognized and Asymptomatic Infection

Approximately 80% of persons seropositive for HSV-2 have never received a diagnosis of genital herpes.[62] Evaluation of persons who have undiagnosed genital HSV-2 shows that 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 mild or unrecognized symptoms.[63] In addition, some symptoms caused by HSV may be mistaken for other disorders, such as vaginitis, hemorrhoids, or an allergic reaction.[63] 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.[37] Initial HSV-2 genital infection in persons with previous HSV-1 antibodies is often asymptomatic. Persons who are seropositive for HSV-2 and unaware of their genital infection account for the majority of persons with genital HSV infection.[40,42] Clinicians should inform and educate these individuals about clinical signs and symptoms of genital herpes, as this may help them recognize the subtle manifestations of symptomatic infection (Figure 10).[Q] Knowledge of HSV-2 Serostatus

Complications of Genital HSV Infection

Aseptic meningitis is a potential complication of genital HSV infection.[50] 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.[58,64] Aseptic meningitis caused by HSV may be severe, often requiring intravenous antiviral therapy, 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.[53,65,66]

Genital HSV Manifestations in Persons with HIV

In the United States, approximately 60% of persons with HIV are HSV-2 seropositive.[1,67,68] When compared to persons without HIV, those with HIV often have more severe and chronic HSV lesions, as well as more asymptomatic shedding of HSV-2 in the genital tract, particularly those with advanced immunosuppression.[69] Individuals with HIV who have a CD4 count of less than 100 cells/mm^3 often have non-healing ulcers and may develop acyclovir-resistant HSV after multiple courses of treatment for herpes.[70,71,72] Treatment of HIV with effective antiretroviral therapy reduces the frequency of symptomatic HSV lesions, but it does not significantly impact HSV-2 mucosal shedding.[73] 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.[74,75] Several studies have reported that persons with HIV and HSV-2 coinfection have a transient increase in HSV-2 genital ulcers following the initiation of antiretroviral therapy.[74,76] Unusual ulcerative lesions can also present as a manifestation of immune reconstitution syndrome.[69]

Genital HSV-2 and Impact on HIV Acquisition and Transmission

Genital HSV-2 infection facilitates both the acquisition and transmission of HIV. The risk of acquiring HIV increases by at least 2-fold in persons with HSV-2 infection, through direct and indirect mechanisms.[77] High-quality data from randomized controlled trials have shown that HSV suppressive therapy does not reduce the risk of 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.[80,81,82] In contrast, persons taking potent, fully suppressive HIV antiretroviral therapy would expect to have negligible changes in genital and plasma HIV RNA levels as a result of an HSV outbreak.[34,83] It remains unknown whether genital HSV-1 infection is associated with a similar increased risk for HIV-1 acquisition.

Laboratory Diagnosis

The clinical diagnosis of genital HSV is challenging because many persons with genital herpes do not develop the characteristic vesicular or ulcerative lesions. Further, less typical lesions, such as fissures, can mimic other infections. Since the natural history and subsequent clinical course depend 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.[5,44]

Virologic Tests

Two types of tests are recommended for the detection of HSV in clinical samples: nucleic acid amplification test (NAAT) methods or viral culture. Among these tests, the NAAT is the preferred test for detecting HSV in clinical samples.[84] Regardless of which test is used, for all samples collected from a lesion, it is important to obtain an adequate quantity of cells by scraping the base of the lesion. Further, if vesicles or pustules are present, they should be unroofed, and the base of the ulcer swabbed to obtain adequate cells for viral culture or PCR.[26] Using the fluid from a vesicular lesion for diagnostic purposes has low yield since HSV is an intracellular virus.

- **Nucleic Acid Amplification Tests**: The nucleic acid amplification tests, such as polymerase chain reaction (PCR) test for HSV DNA, are the preferred methods of diagnosing HSV in clinical samples, primarily because of the very high sensitivity (90.9-100%) and high specificity with this technique.[84,85,86] When compared with culture, the sensitivity of HSV PCR is significantly higher. Most commercially available PCR assays can differentiate HSV-1 from HSV-2 infection.[87,88] For adults and children with suspected HSV CNS infection, PCR is the preferred test for detecting HSV in cerebrospinal fluid.[89]
- **Viral Culture**: Prior to the availability of PCR testing, viral culture was the gold standard for diagnosing HSV from a clinical specimen. Viral culture is highly specific, but sensitivity rapidly declines 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.[90] For recurrent HSV infection, HSV is isolated in only 25 to 50% of lesions.[90] Isolates from culture can be typed as HSV-1 or HSV-2.
- **Antigen Detection**: The use of direct fluorescent antibody (DFA) testing offers lower sensitivity than viral culture or PCR and is not recommended.[26,91]
- **Cytologic Examination**: Cells infected with HSV will show characteristic changes, and these can be observed by obtaining a sample from the lesion and smearing it on a microscope slide (e.g., Tzanck smear). This test is not recommended due to low sensitivity (less than 80%) and inability to differentiate between HSV-1 and HSV-2.[Q] Laboratory Diagnostic Techniques

Type-Specific Serologic Tests

Two types of HSV serologic tests are commercially available: type-common and type-specific.[84] Type-specific serologic tests are based on antigens specific for HSV-1 (gG1) and HSV-2 (gG2), and these tests are preferred since they can distinguish antibodies to HSV-2 from antibodies to HSV-1.[26] Type-common serologic tests do not distinguish HSV-2 from HSV-1. Because HSV-2 infections are usually sexually acquired, and HSV-2 only rarely causes oral disease, the presence of type-specific HSV-2 antibodies nearly always indicates anogenital herpes infection.[84] In contrast, the presence of HSV-1 antibody does not distinguish anogenital from orolabial HSV-1 infection. Antibodies to HSV develop during the first several weeks following infection and persist indefinitely. The type-specific assays commonly used in clinical practice are the enzyme-linked immunosorbent (ELISA) IgG assays and Western blot assays. The use of HSV IgM antibody assays is not recommended for the serodiagnosis of genital herpes since they have low sensitivity and specificity.[84]

Performance of Type-Specific HSV Serologic Assays

Multiple laboratory-based HSV-2 serologic assays are available and FDA-approved for the diagnosis of HSV

infection. The sensitivities of these tests for the detection of HSV-2 antibodies have been reported in studies to vary from 80 to 98%.[92,93,94] The most common cause of a false-negative result is testing performed early after HSV acquisition, since HSV-specific antibodies can take from 2 weeks to 3 months to develop.[95] In a recent study, investigators compared three FDA-cleared HSV-1/HSV-2 IgG antibody assays with the gold-standard Western blot test in 1,994 individuals, 53% of whom had a previously confirmed diagnosis of HSV-1 and/or HSV-2 (based on PCR or culture).[96] Overall, the specificity for HSV-2 ranged from 94.2% to 99.5%, with the lowest specificity among samples with index values less than 3.0.[96] In addition, all assays had relatively low specificity for HSV-1, ranging from 80.5% to 92.1%, confirming that better serologic diagnostic tests are needed.

Two-Step Type-Specific Serologic Testing

For clinical purposes, serologic testing for HSV-2 should use type-specific assays, with a two-step process that consists of performing an initial test followed by a second confirmatory test for all positive results on the initial test; the confirmatory test should utilize a technology distinct from that used for the initial test.[84] Negative tests do not require confirmatory testing unless recent HSV-2 infection is suspected. For persons with suspected recent HSV infection, the initial test should be repeated in approximately 12 weeks.

- **Initial Test**: In the United States, the most commonly used initial serologic tests are the enzyme-linked immunoassays or chemiluminescence-linked immunoassays. These assays, which detect IgG antibodies to HSV-2 glycoprotein-G antigen, have high sensitivity, except in very early HSV-2 infection. The major limitation of these tests, such as the *HerpeSelect* assay, is poor specificity (false-positive tests), particularly in persons who have a positive low index value (1.1-3.0).[96,97,98] The significant false-positive rate with low index values when using this test is a major reason for the recommendation to perform confirmatory testing.[84]
- **Confirmatory Test**: Confirmatory HSV-2 serologic testing should utilize a second test that has a method distinct from that used for the initial test. The only available HSV-2 confirmatory test is the Western blot, which has limited access (available through the University of Washington). If the *HerpeSelect* HSV-2 ELISA is used as the initial test, the *HerpeSelect* HSV-2 immunoblot is not recommended as the confirmatory test, since these two assays share use of the same HSV-2 antigen. In many settings, confirmatory testing is not available. In such situations, patients and providers should understand the limitations of the available testing and the potential for false-positive results prior to performing the tests. If confirmatory tests are unavailable, it is recommended to counsel persons undergoing herpes testing about the limitations of available testing, including problems with false-positive results, before ordering the initial serologic test.[84]

Screening for HSV-2 Infection

The following summarizes recommendations, as outlined in the 2021 STI Treatment Guidelines, for herpes screening with type-specific serologic assays in the general population and in specific groups that may have unique risks for acquiring HSV-2:[99]

General Population [99]

Screening for HSV-1 or HSV-2 infections in asymptomatic persons with type-specific serologic testing is not recommended for the general population.[99,100,101] Nonetheless, HSV type-specific serologic assays can be useful in the following scenarios:[84]

- For persons who have recurrent or atypical genital symptoms with negative HSV PCR or culture results
- For persons who have a clinical diagnosis of genital herpes without laboratory PCR or culture confirmation
- For persons with a sex partner who has genital herpes (serologic studies are performed in this setting to determine the risk of infection and to guide counseling)
- Persons considered to have a higher risk for HSV-2 infection (e.g., persons presenting for an STI evaluation, especially those with 10 or more lifetime sex partners, and persons with HIV)

Women [99]

- Type-specific HSV serologic testing is not routinely recommended for women, but it can be considered for women presenting for an STI evaluation, especially for women with 10 or more sex partners.

Pregnant Women [99,102]

- For pregnant women who do not have genitourinary symptoms, routine screening with type-specific HSV serologic testing is not recommended. Testing might be useful for identifying pregnant women at risk for acquiring HSV infection and guiding counseling to prevent acquisition of HSV during pregnancy.

Men Who Have Sex Only with Women [99]

- For men who only have sex with women, type-specific HSV serologic testing can be considered for individuals presenting for an STI evaluation, especially men who have 10 or more sex partners.

Men Who Have Sex with Men [99,103]

- For MSM, routine screening with type-specific HSV serologic tests can be considered if the herpes infection status is unknown and the individual had a previously undiagnosed genital tract infection.

Persons with HIV [99]

- For persons with HIV, type-specific HSV serologic testing can be considered for those who present for an STI evaluation (especially for those persons with more than 10 sex partners) [Q] Routine Serologic Screening for HSV

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.[84,104,105]

Antiviral Agents Used to Treat HSV

Antiviral therapy for oral and genital HSV infection includes three oral medications: acyclovir, valacyclovir, and famciclovir. The compounds acyclovir and penciclovir are nucleoside analogues that require triphosphorylation to inhibit HSV (Figure 11).[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 anti-herpes activity by selectively inhibiting HSV DNA polymerase.[109] Valacyclovir and famciclovir are prodrugs that undergo conversion as first-pass metabolism in the liver, with valacyclovir converted to acyclovir and famciclovir converted to penciclovir.

First Clinical Episode

Antiviral therapy may have a major impact on symptoms for individuals with a first clinical episode of genital HSV, especially if the duration of symptoms is less than 7 days at the time antiviral therapy is started. Therapy should be empirically started if genital herpes is suspected, rather than waiting for confirmatory laboratory results. 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.[110,111,112] The recommended treatment for a first clinical episode of genital herpes is a 7- to 10-day course with acyclovir, famciclovir, or valacyclovir.[84] Treatment may be extended if healing is incomplete after 10 days of therapy. All of these antiviral medications have been shown to shorten the duration of viral shedding, improve symptoms, and accelerate healing.[84,111,113,114]

Table 1. 2021 STI Treatment Guidelines: Genital Herpes
Treatment of First Clinical Episode of Genital Herpes

For all recommended regimens, note that treatment can be extended if healing is incomplete after 10 days of therapy.

Recommended Regimens
Acyclovir *400 mg orally three times a day for 7–10 days*

Recommended Regimens
Famciclovir *250 mg orally three times a day for 7–10 days*

Recommended Regimens

Valacyclovir *1 g orally twice a day for 7–10 days*

Acyclovir 200 mg orally five times/day is also effective but is not recommended because of the frequency of dosing.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Recurrent Episodes

Most persons 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 and decrease the risk of transmission).[84]

Episodic Therapy for Recurrent Genital Herpes

Optimal episodic treatment requires initiation of therapy as soon as prodromal symptoms are present or within one day of lesion onset. Persons with recurrent herpes ideally receive an antiviral prescription with instructions to self-initiate treatment promptly with the onset of prodromal symptoms that are consistent with genital herpes. Acyclovir, famciclovir, and valacyclovir are effective for episodic treatment of genital herpes, and clinical trials have established efficacy with multiple different dosing options.[77,114,115,116,117,118]

Table 2. 2021 STI Treatment Guidelines: Genital Herpes Episodic Therapy for Recurrent HSV-2 Genital Herpes

Recommended Regimens
Acyclovir *800 mg orally twice a day for 5 days*

Recommended Regimens
Acyclovir *800 mg orally three times a day for 2 days*

Recommended Regimens
Famciclovir *1 g orally twice daily for 1 day*

Recommended Regimens

Famciclovir
500 mg orally once, followed by 250 mg orally twice daily for 2 days

Recommended Regimens

Famciclovir
125 mg orally twice daily for 5 days

Recommended Regimens

Valacyclovir
500 mg orally twice a day for 3 days

Recommended Regimens

Valacyclovir
1 g orally once a day for 5 days

Acyclovir 400 mg orally 3 times/day is also effective, but is not recommended because of frequency of dosing.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

[Q] Episodic Therapy for Recurrent Genital Herpes

Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy with either acyclovir,[119,120,121] valacyclovir,[43,122,123,124] or famciclovir[43,125,126] delays the time to first genital herpes recurrence and reduces the frequency of recurrences by approximately 70 to 85%. Two meta-analyses of HSV treatment showed similar results with these antiviral medications.[127,128] Quality of life is often improved for persons with frequent herpes recurrences who receive suppressive therapy when compared with episodic therapy.[122,129] Persons with 10 or more recurrences per year may benefit from increased doses of valacyclovir (1 gram daily) to suppress genital herpes recurrences.[84,124] There is no evidence that long-term suppressive therapy in immunocompetent persons leads to antiviral resistance. Since the frequency of recurrences may diminish over time, clinicians should periodically reassess the need for continued suppressive therapy. Suppressive therapy with valacyclovir (500 mg daily) reduces the risk of transmission of HSV-2 to partners who are HSV-seronegative by about 50%.[130] The recommended daily suppressive therapy regimens include various dosing strategies for valacyclovir, famciclovir, and acyclovir.[84]

Table 3. 2021 STI Treatment Guidelines: Genital Herpes Suppressive Therapy for Recurrent HSV-2 Genital Herpes

Recommended Regimens

Acyclovir
400 mg orally twice a day

Recommended Regimens

Valacyclovir
500 mg orally once a day

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).

Recommended Regimens

Valacyclovir
1 g orally once a day

Recommended Regimens

Famciclovir
250 mg orally twice a day

Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because the frequency of genital HSV-2 recurrence diminishes over time for many persons.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

[Q] Suppressive Antiviral Therapy for HSV-2

Treatment of Severe Disease

Intravenous (IV) acyclovir should be provided for persons 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).[84] The recommended regimen is acyclovir 5 to 10 mg/kg intravenously every 8 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 individuals with impaired renal function.

Genital HSV in Persons with HIV

Antiviral therapy has been found to be safe and effective for episodic and suppressive therapy of genital herpes in persons with HIV.[69,131,132]

Episodic Therapy for Recurrent Genital Herpes in Persons with HIV

Since individuals with HIV may have severe, prolonged cases of orolabial, genital, and perianal HSV infections, the recommended episodic therapy options utilize higher doses and longer courses of antiviral medications.[84]

Table 4. 2021 STI Treatment Guidelines: Genital Herpes

Episodic Therapy for Recurrent Genital Herpes Among Persons with HIV*

Recommended Regimens
Acyclovir *400 mg orally three times a day for 5–10 days*

Recommended Regimens
Famciclovir *500 mg orally twice a day for 5–10 days*

Recommended Regimens
Valacyclovir *1 g orally twice a day for 5–10 days*

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

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Suppressive Therapy for Genital Herpes in Persons with HIV

In persons with HIV, suppressive therapy with acyclovir, valacyclovir, or famciclovir is effective in decreasing HSV outbreaks.[84,132,133,134] Unlike in HSV-2 serodifferent couples without HIV, in whom antiviral treatment significantly reduces HSV-2 transmission to the susceptible partner, treatment of persons with HIV-1 and HSV-2 coinfection with daily suppressive antiviral therapy does not reduce the transmission of HSV-2 to susceptible partners.[130,135] Persons with HIV who have a CD4 count of less than 250 cells/mm^3 have a significant increase in genital herpes recurrences in the first 6 months after starting antiretroviral therapy; to prevent these recurrences, some experts recommend suppressive therapy during this 6-month period.[84] There are several recommended options for suppressive therapy in persons with HIV, but all require at least twice-daily dosing.[84]

Table 5. 2021 STI Treatment Guidelines: Genital Herpes Daily Suppressive Therapy Among Persons with HIV

Recommended Regimens
Acyclovir *400–800 mg orally two to three times a day*

Recommended Regimens
Famciclovir *500 mg orally twice a day*

Recommended Regimens

Valacyclovir
500 mg orally twice a day

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Antiviral-Resistant HSV

Development of antiviral-resistant HSV is rare among immunocompetent persons, even those who take long-term HSV suppressive therapy.[72] Most cases of antiviral-resistant HSV have occurred in severely immunocompromised individuals.[70] Antiviral-resistant HSV most often results from absent or decreased production of viral thymidine kinase (TK-negative mutants) (Figure 12).[70,109] The oral antiviral agents used to treat genital HSV—acyclovir, famciclovir, and valacyclovir—all require activation by HSV thymidine kinase and, therefore, are ineffective against TK-negative mutants. Foscarnet bypasses the thymidine kinase cascade and directly inhibits the viral DNA polymerase; it is highly effective against antiviral-resistant HSV.[136,137] Cidofovir does not require activation by viral thymidine kinase, and both intravenous and topical forms of this drug have been successfully used to treat antiviral-resistant HSV.[138,139,140] Topical imiquimod has also been effective in persons with HIV who have antiviral-resistant HSV-2 infections, but experience is limited.[141,142] The following list includes the options for the treatment of antiviral-resistant genital HSV, but management should involve consultation with an infectious diseases specialist.[84]

- **Foscarnet**: The treatment of choice for antiviral-resistant HSV is foscarnet 40-80 mg/kg body weight IV every 8 hours until clinical resolution is attained. Foscarnet can potentially cause severe adverse effects, including nephrotoxicity and electrolyte disturbances.
- **Cidofovir**: 5 mg/kg body weight IV once weekly until clinical resolution is attained. Note that cidofovir can cause severe renal abnormalities.
- **Imiquimod 5% cream**: Apply to lesions and leave on for 8 hours 3 times per week until clinical resolution.
- **Cidofovir 1% gel**: Apply to lesions 2–4 times daily until clinical resolution is attained. This preparation is not commercially available and must be compounded by a pharmacist.

Genital HSV in Pregnancy and Neonatal Herpes

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.[143] Neonatal HSV infrequently occurs, with an estimated incidence of 1 in 3,000 deliveries.[143,144] In the United States, however, HSV-related neonatal deaths increased significantly between 1995 and 2017.[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 highest among pregnant women who newly acquire genital HSV-2 (or HSV-1) late in pregnancy when compared to women who have reactivation of genital HSV during pregnancy.[143] The highest HSV transmission risk occurs when a pregnant woman acquires HSV near the time of delivery.[147,148,149] If a pregnant woman has primary genital HSV infection 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 they are shedding HSV during a recurrent episode of genital herpes.[146] The following five factors have been identified as the major influences on the risk of transmission:[146]

- Whether the HSV infection is primary or recurrent
- HSV antibody status of the pregnant woman
- Duration of membrane rupture
- Integrity of mucocutaneous barrier (e.g., use of fetal scalp electrodes)
- Mode of delivery (vaginal versus cesarean)

General Approach to Preventing Neonatal HSV Infection

Strategies used to prevent neonatal herpes depend on preventing the 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.[84] All pregnant women should be questioned about a history or symptoms of genital herpes, but routine type-specific HSV antibody screening of pregnant women is not recommended.[84,150] When women with a history of genital herpes present in labor, the clinician should carefully ask them whether they have any active genital lesions or prodromal genital symptoms consistent with a herpes outbreak.[84] It is important that optimal prevention measures are utilized to prevent HSV transmission and 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 HSV
- 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 neonate 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.[53,84] In addition, if possible, use of invasive monitoring during labor should be limited.[84,149] 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.[84,152] All women who are pregnant should be asked early in pregnancy about symptoms of genital herpes, including prodromal symptoms.[152] 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 sex partner known or thought to have genital herpes.[84] 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.[84] The use of suppressive antiviral therapy is not recommended for women who are HSV-seropositive but have no history of genital HSV outbreaks.[84]

Asymptomatic Women with a History of Recurrent Genital HSV

Prophylactic suppressive therapy with acyclovir or valacyclovir beginning at 36 weeks of gestation should be offered to all women with a history of genital herpes, since it has been shown to reduce HSV recurrences at delivery by 75%, decrease the need for cesarean delivery for recurrent genital herpes by 40%, and lessen HSV shedding at delivery.[84,153,154] Use of suppressive therapy does not completely eliminate HSV shedding late in pregnancy, and cases of neonatal HSV transmission have occurred despite maternal prenatal antiviral suppressive therapy.[153,155,156] Suppressive treatment can be stopped after delivery. Studies of pregnancy outcomes following prenatal acyclovir exposure have not identified an increased risk of congenital disabilities.[157] Viral vaginal cultures obtained during pregnancy do not predict the risk of exposure to HSV at delivery.[158] Therefore, routine viral cultures of asymptomatic pregnant women with a history of recurrent genital herpes are not recommended.[84] Note that higher doses of acyclovir or valacyclovir are required for suppressive therapy in pregnancy due to enhanced renal excretion of these medications.[84]

Table 6. 2021 STI Treatment Guidelines: Genital Herpes Suppression of Recurrent Genital Herpes Among Pregnant Women*

*Treatment recommended starting at 36 weeks of gestation

Recommended Regimens
Acyclovir *400 mg orally three times a day*

Recommended Regimens
Valacyclovir *500 mg orally twice a day*

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

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. As noted above, in this situation, cesarean section (ideally, before rupture of membranes) is recommended for any pregnant woman with active genital herpes lesions or prodromal symptoms at the time of delivery.[154] In addition, if possible, use of invasive monitors during delivery should be limited.[149] Delivery by cesarean section does not completely eliminate the risk for HSV transmission to the infant.[151,154] Most experts recommend that women with first-episode genital HSV infection near term should be managed in consultation with maternal-fetal medicine and infectious diseases specialists; for those women who acquire HSV in the third trimester, cesarean section may be offered.[152] The initial management should include prompt antiviral treatment of the genital HSV infection.[Q] Risk of Perinatal HSV-2 Transmission

Clinical Manifestations of Neonatal Herpes

Neonatal herpes infection is a rare complication of maternal genital herpes infection, occurring in about 1 in 3,000 deliveries in the United States; it is most likely to occur in women who acquire primary genital herpes infection at or near the time of delivery.[147,159] 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.[149] Among all cases of vertical HSV transmission, an estimated 85% occur during labor and delivery, 5% in utero, and 10% in the postpartum period.[159,160] Neonatal herpes includes three categories:[159,160,161]

- **Skin, eye, and/or mouth (SEM)**: Infants with SEM account for about 45% of cases of neonatal herpes, and these infants usually present with SEM 10–12 days after birth. Approximately 80% of the infants with SEM will have multiple vesicular skin lesions evident on physical examination.
- **Disseminated Disease**: Infants with disseminated disease typically present 10–12 days after birth and account for about 25% of cases of neonatal herpes. Disseminated disease may involve multiple organ systems, including the liver, lungs, and central nervous system. Most infants with disseminated HSV disease also have vesicular skin lesions, but about 40% never have evidence of skin lesions.
- **Isolated Central Nervous System Disease**: Infants who develop central nervous system disease usually present with encephalitis 16–19 days after birth. Isolated central nervous system disease accounts for about 35% of cases of neonatal herpes. Clinical manifestations of neonatal HSV central nervous system disease can include lethargy, irritability, poor feeding, temperature instability, and seizures.
- **Birth Weight and Gestational Age**: In a multivariate regression analysis of all infants in a neonatal intensive care unit who received acyclovir, those who were diagnosed with herpes simplex infection had lower gestational age, lower birth rate, and increased morbidity and mortality.[162]
- **Infant Mortality**: With improved diagnosis and high-dose acyclovir treatment, infant mortality has declined from greater than 20% in the 1980s to approximately 6% in 2016.[163] With disseminated infection, however, infant death rates remain high.[163]

Management of Neonatal Herpes

Infants with HSV disease should be treated with parenteral acyclovir therapy in consultation with a pediatric infectious diseases specialist. Despite improvement in outcomes with parenteral acyclovir and subsequent suppressive oral acyclovir therapy, neurodevelopmental outcomes remain poor in neonates with central nervous system herpes if present at birth.[159,164] Treatment duration is generally 14 days for SEM disease or 21 days for disseminated and central nervous system disease, and suppressive therapy after central nervous system 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.[84,164]

Table 7. 2021 STI Treatment Guidelines: Genital Herpes
Treatment of Neonatal Herpes

Recommended Regimen for Infants with Neonatal Herpes Limited to the Skin and Mucous Membranes
Acyclovir *20 mg/kg body weight IV every 8 hours for 14 days*

Recommended Regimen for Infants with Neonatal Herpes who have Disseminated Disease and Disease Involving the Central Nervous System
Acyclovir *20 mg/kg body weight IV every 8 hours for 21 days*

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Prevention

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

Suppressive Antiviral Therapy

In heterosexual HSV-2 serodifferent partnerships, daily suppressive therapy with valacyclovir reduces the risk of HSV transmission between partners. This was shown in a large, randomized trial that enrolled 1,484 HIV-seronegative, heterosexual HSV-2 serodifferent sex 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 the partners randomized to placebo (48% reduction). (Figure 14).[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, taken by the person with genital herpes, did not prevent transmission of HSV-2 to susceptible heterosexual partners.[135] These studies, taken together, suggest suppressive antiviral therapy is effective for preventing transmission of HSV-2 among HIV-seronegative persons, but is not effective in HIV-seropositive persons.

Prophylactic Antiviral Therapy

The use of anti-herpes antiviral medications (acyclovir, famciclovir, or valacyclovir) by persons without HSV-2 to prevent acquisition of HSV-2 has not been studied. Accordingly, use of these antivirals for HSV-2 preexposure prophylaxis (PrEP) is not recommended.

Tenofovir DF

Tenofovir disoproxil fumarate (tenofovir DF) is a nucleotide reverse transcriptase inhibitor frequently used both for HIV treatment and HIV PrEP.[165,166,167,168] Several HIV treatment and PrEP studies have also examined the impact of tenofovir DF on HSV-2 acquisition and transmission. The potential for tenofovir DF to reduce HSV-2 acquisition was first identified in two HIV PrEP studies that found tenofovir 1% vaginal gel reduced HSV-2 acquisition in women.[169,170] In contrast, among HSV-2 seropositive women, HSV-2 shedding or genital lesion rate was not impacted by either oral tenofovir or tenofovir gel.[171] In an HIV PrEP study that enrolled heterosexual men and women in Africa, the use of oral tenofovir DF or tenofovir DF-emtricitabine was associated with a 30% decrease in the acquisition of HSV-2.[172] In a separate HIV PrEP study that enrolled MSM, daily oral tenofovir DF-emtricitabine reduced episodes of symptomatic genital ulcers, but there was no impact on HSV-2 acquisition.[173] In addition, in a study of persons with HIV who were taking tenofovir DF as part of an antiretroviral regimen, there was no impact on preventing hSV-2 acquisition.[174] At this time, there are insufficient data to recommend tenofovir DF for the purpose of preventing the acquisition or transmission of HSV-2.[84] Further, tenofovir (in any form) is not FDA-approved for the prevention or treatment of HSV-2 or HSV-1.

Condoms

Several studies have examined the efficacy of condoms to prevent HSV-2 transmission.[38,175] In a pooled analysis of 6 prospective studies, consistent use of condoms reduced the risk of HSV-2 transmission by 30%.[176] 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. Therefore, condoms can play a 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-serodifferent partners.[177] In a study that enrolled 199 adults 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.[177]

Male Circumcision

Male circumcision is an underutilized strategy for the prevention of sexually transmitted infections in men and their female sex partners. Male circumcision significantly reduces the incidence of HSV-2 acquisition in men without HIV: in two independent randomized trials of male circumcision in Rakai, Uganda, male circumcision was found to reduce HSV-2 seroconversion by 25%.[178,179]

Patient Counseling and Education

Counseling plays an integral role in the management of persons 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. Persons with genital herpes may experience significant stress burden related to the incurable nature of the infection and the need for disclosure to sex partners.[180] Counseling has two main goals: (1) to help individuals diagnosed with genital herpes better understand and cope with this chronic infection, and (2) to prevent sexual and perinatal HSV transmission. The following are specific counseling recommendations directly from the 2021 STI Treatment Guidelines.[84]

Symptomatic HSV-2 Genital Herpes

When counseling persons with symptomatic HSV-2 genital herpes infection, the provider should discuss the following:

- The natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and the attendant risks for sexual transmission of HSV to occur during asymptomatic periods (asymptomatic viral shedding is most frequent during the first 12 months after acquiring HSV-2).
- The effectiveness of daily suppressive antiviral therapy for preventing symptomatic recurrent episodes of genital herpes for persons experiencing a first episode or recurrent genital herpes.
- The effectiveness of daily use of valacyclovir in reducing risk for transmission of HSV-2 among persons without HIV and use of episodic therapy to shorten the duration of recurrent episodes.
- The importance of informing current sex partners about genital herpes and informing future partners before initiating a sexual relationship.
- The importance of abstaining from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
- The effectiveness of male latex condoms, which, when used consistently and correctly, can reduce, but not eliminate, the risk for genital herpes transmission.
- The type-specific serologic testing of partners of persons with symptomatic HSV-2 genital herpes to determine whether such partners are already HSV seropositive or whether the risk of acquiring HSV exists.
- The low risk for neonatal HSV except when genital herpes is acquired late in pregnancy or if prodrome or lesions are present at delivery.
- The increased risk of HIV acquisition among HSV-2 seropositive persons who are exposed to HIV.
- The lack of effectiveness of episodic or suppressive therapy among persons with HIV to reduce the risk of transmission to partners who might be at risk for HSV-2 acquisition.

Asymptomatic HSV-2 Genital Herpes

When counseling persons with asymptomatic HSV-2 genital herpes infection, the provider should consider the following:

- Asymptomatic persons who receive a diagnosis of HSV-2 by type-specific serologic testing (with confirmatory testing, if needed) should receive education about the symptoms of genital herpes infection.
- Episodic and suppressive antiviral therapies are used predominantly to treat recurrences, prevent recurrences, and prevent transmission to sex partners of persons with symptomatic HSV-2 infection.
- For patients with serological evidence of HSV-2 (with combination testing if needed) without symptomatic recurrences, neither episodic nor suppressive therapy is indicated for prevention of recurrences.
- Among persons with asymptomatic infection, the efficacy of suppressive therapy to prevent HSV-2

transmission to sex partners has not been studied.
- Because of the decreased risk for shedding among those with asymptomatic HSV-2 genital herpes, the benefit of suppressive therapy for preventing transmission is unknown among this population.

HSV-1 Genital Herpes

When counseling persons with HSV-1 genital herpes infection, the provider should consider the following:

- Persons with virologic laboratory-documented symptomatic HSV-1 genital herpes infection should be educated that the risk of recurrent genital herpes and genital shedding is lower with HSV-1 infection compared with HSV-2 infection.
- Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences.
- For patients with frequently recurring HSV-1 genital herpes, suppressive therapy might be considered. Suppressive therapy to prevent HSV-1 transmission to sex partners has not been studied.

Counseling for Suppressive Antiviral Therapy

For persons with symptomatic HSV-1 genital herpes or asymptomatic HSV-2 genital herpes, suppressive therapy can be considered for those who have substantial psychosocial distress caused by the diagnosis of genital herpes. For women who have genital herpes, the providers who care for them during pregnancy and those who will care for their newborn infant should be informed of their infection.

Nature of the Disease

- HSV-2 is the most common cause of recurrent genital herpes.
- Asymptomatic or subclinical infection is common, and more than 85% of persons with HSV-2 have not been diagnosed.
- The clinical manifestations of herpes infection vary significantly with the first clinical episode when compared with recurrent infections.
- 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 sex partners.

Transmission Issues

- Sexual transmission of HSV-1 and HSV-2 can occur through genital-to-genital, oral-to-genital, genital-to-oral, anal-to-genital, and genital-to-anal 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 area in women and the 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.
- 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 receive education regarding 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.[181,182,183] 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.

Counseling Pregnant Women

- Ask all pregnant women whether they have a history of (or symptoms of) genital herpes.
- Women without a history of genital herpes should receive counseling 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.

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.
- Genital herpes is a chronic viral infection predominantly caused by HSV-2; it is characterized by periods of latency punctuated by periods of viral shedding.
- More than 85% of persons with genital herpes are unaware of their infection, and asymptomatic shedding of HSV accounts for most transmitted genital HSV infections.
- To make a clinical diagnosis of genital herpes, a direct viral test (preferably PCR) should be performed on a sample taken from a lesion.
- Routine serologic screening for genital herpes is not recommended for the general population, but type-specific serologic screening for HSV-2 may be indicated in certain situations.
- When type-specific serologic testing is indicated, a two-step process should be utilized to confirm a low index value (less than or equal to 3.0) on initial EIA or CLIA testing.
- Antiviral therapy with acyclovir, valacyclovir, or famciclovir can be used intermittently for each episode of genital herpes (episodic therapy) and to prevent recurrent outbreaks (suppressive therapy).
- Among persons without HIV, daily suppressive therapy with valacyclovir prevents recurrent outbreaks of genital herpes and reduces transmission of HSV-2 to sex partners.
- Prophylactic therapy with acyclovir or valacyclovir beginning at 36 weeks of 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 and thereby reduce the need for a cesarean 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 sex partners.

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Figures

Figure 1 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.

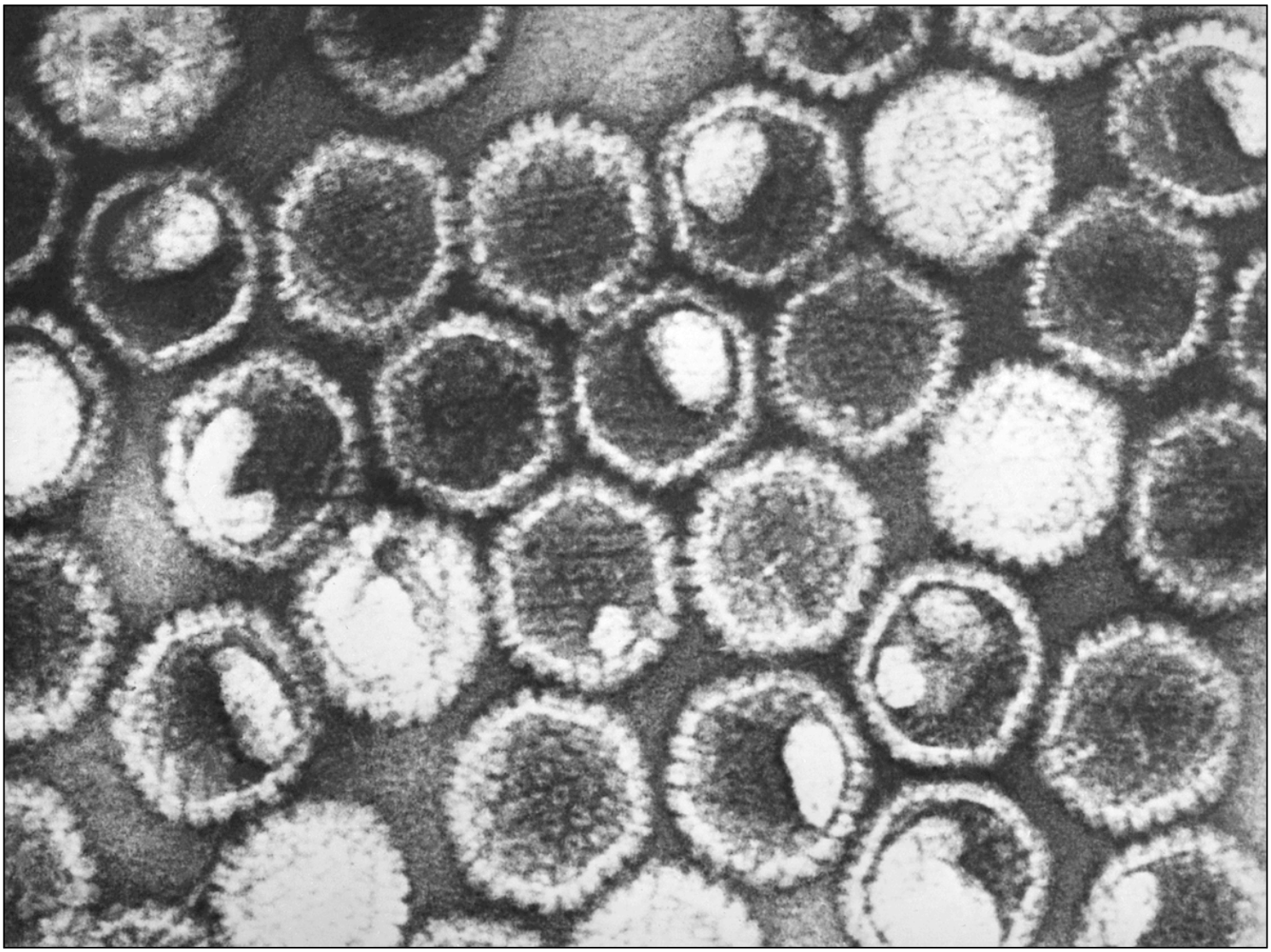


Figure 2 HSV-2 Seroprevalence in the United States

Source: McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. NCHS Data Brief. 2018:1-8.

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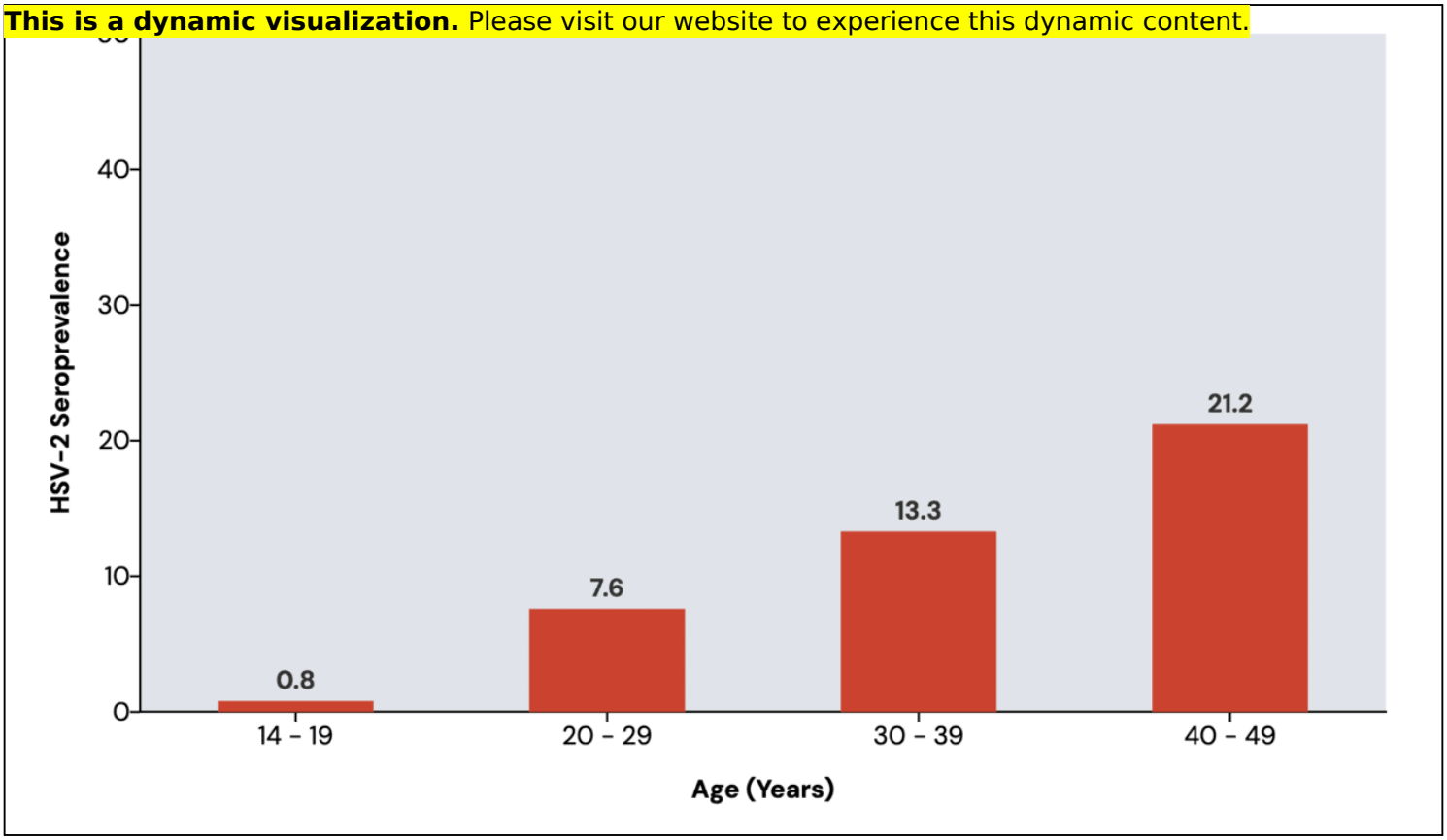


Figure 3 HSV-1 Seroprevalence in the United States

Source: McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. NCHS Data Brief. 2018:1-8.

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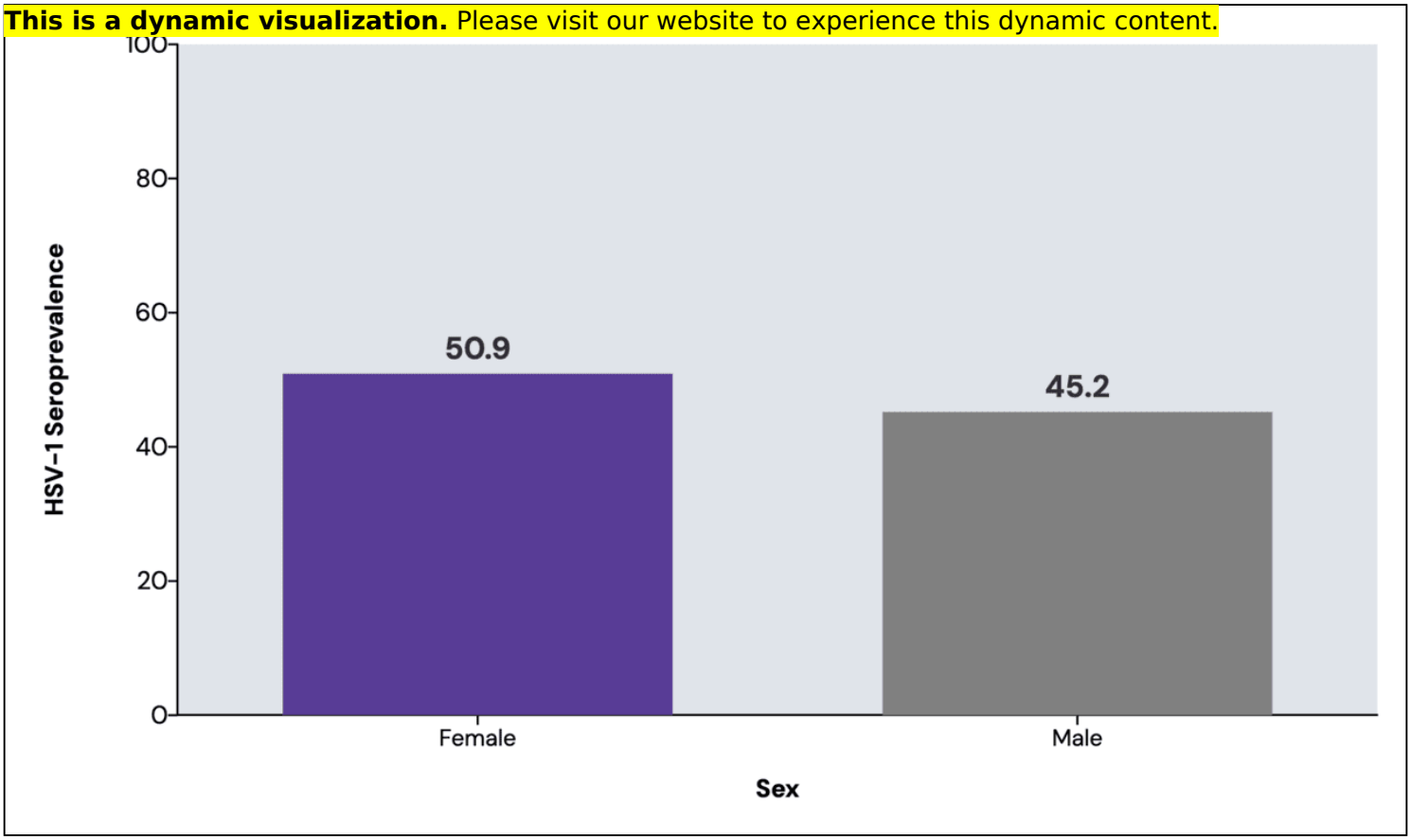


Figure 4 Basic Structure of Herpes Simplex Virus

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

Illustration by Jared Travnicek, Cognition Studio

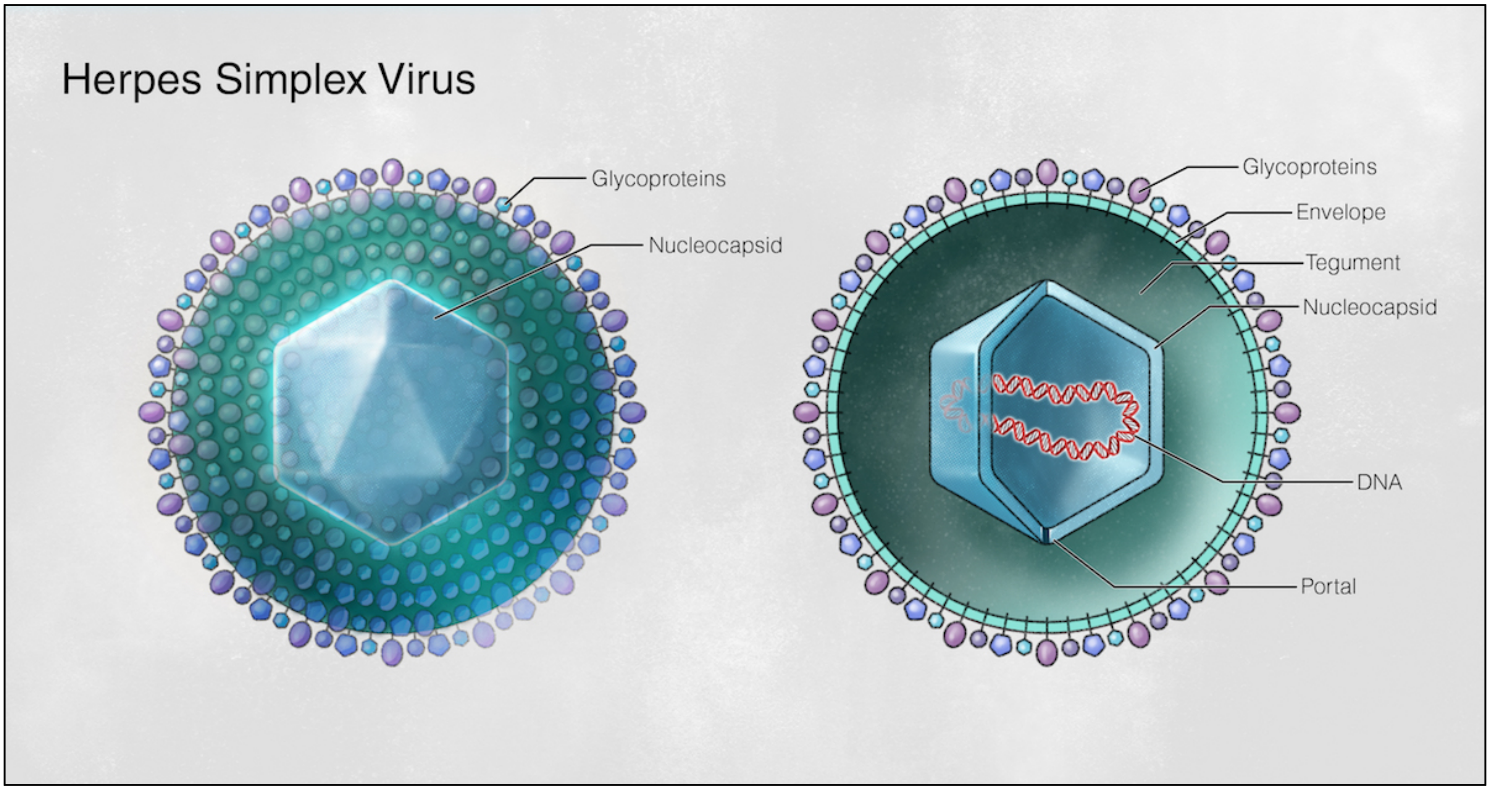


Figure 5 Duration of Genital HSV-2 Shedding per Episode

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.

Source: Mark KE, Wald A, Magaret AS, et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. J Infect Dis. 2008;198:1141-9.

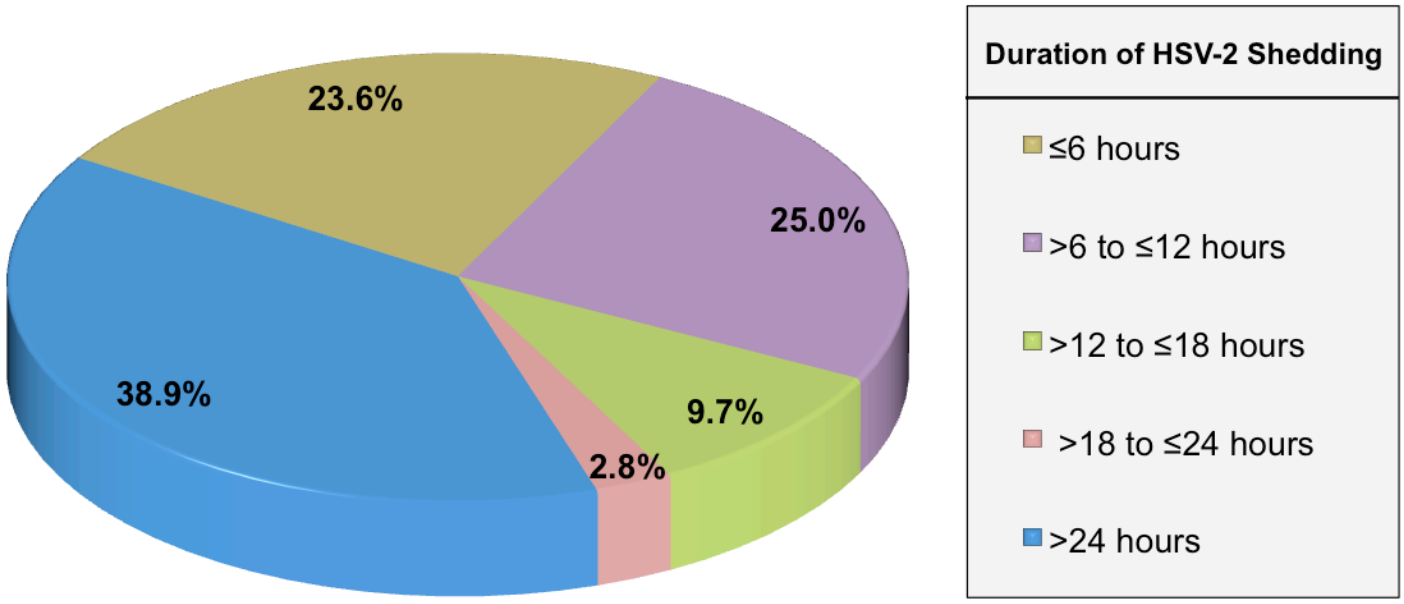


Figure 6 Oral and Ano-Genital Transmission of HSV-1 and HSV-2

Source: adapted from Van Wagoner N, Qushair F, Johnston C. Genital Herpes Infection: Progress and Problems. Infect Dis Clin North Am. 2023;37:351-67.

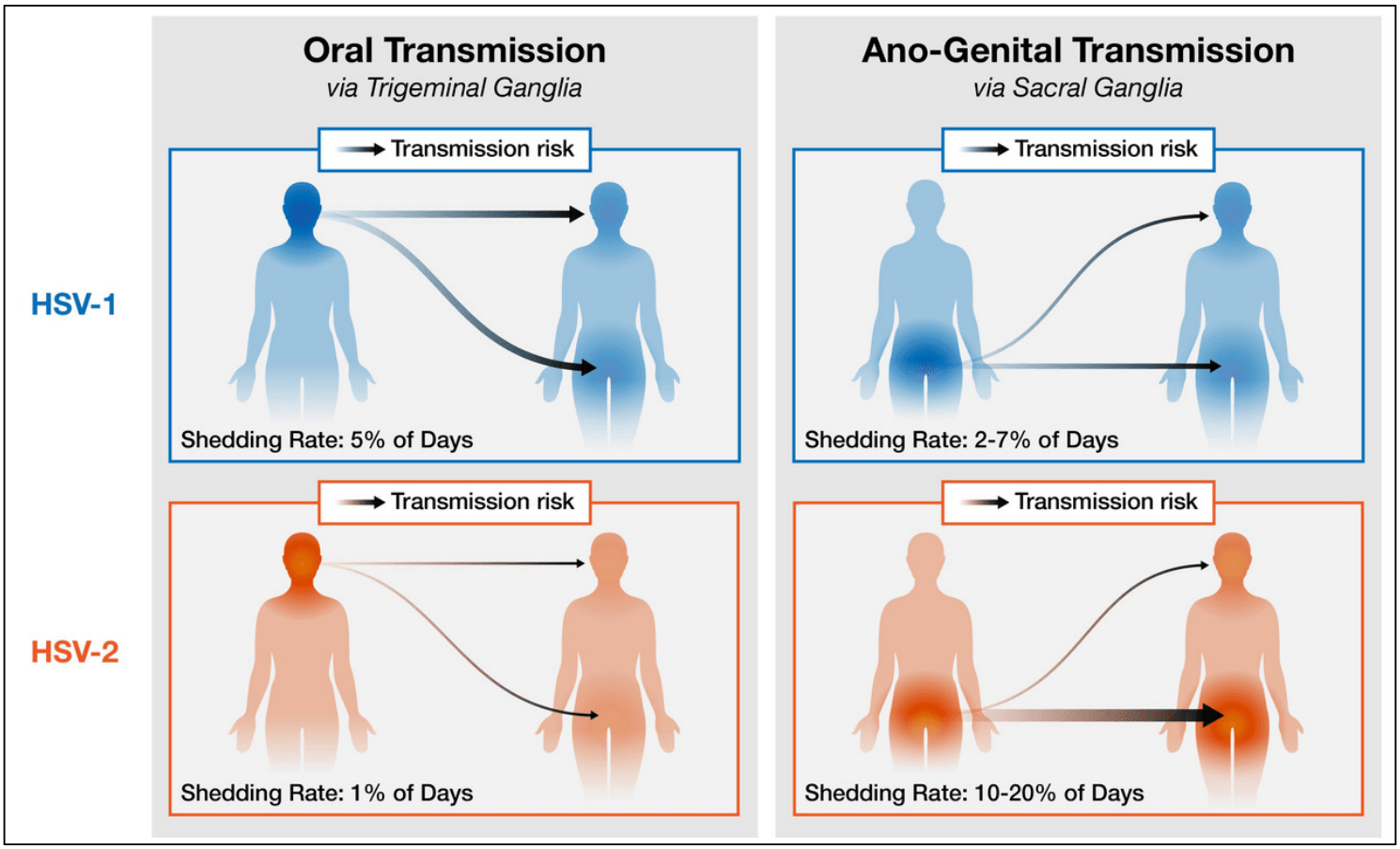


Figure 7 Primary Genital HSV Infection

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.

Source: Kimberlin DW, Rouse DJ. Clinical practice. Genital herpes. N Engl J Med. 2004;350:1970-7. This figure was originally adapted from Corey L, Wald A. Genital herpes. In: Holmes KK, Mardh P-A, Sparling PF, et al., eds. Sexually transmitted diseases. 3rd ed. New York: McGraw-Hill, 1999:285-312. ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

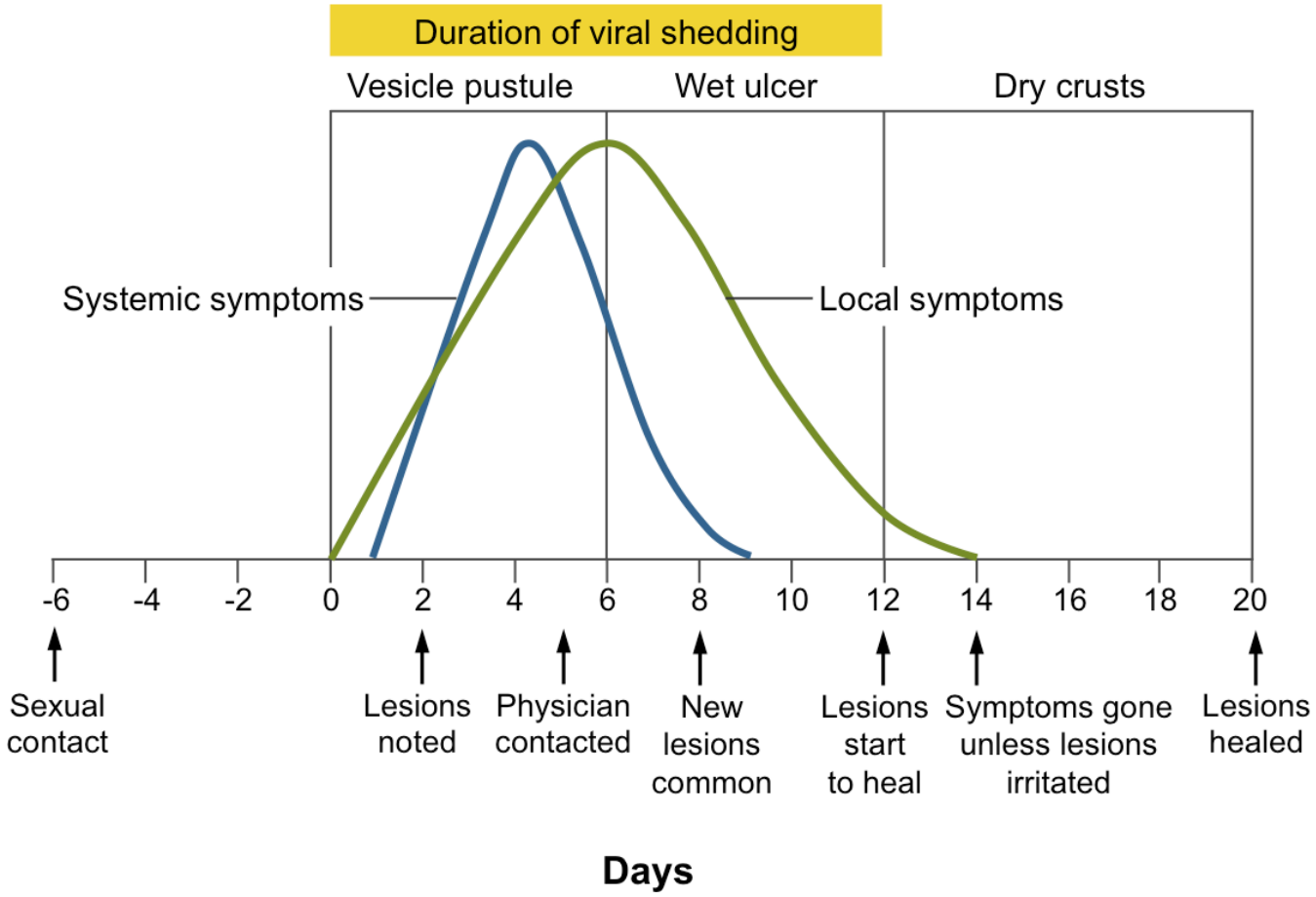


Figure 9 (Image Series) - Recurrent Genital Herpes: Manifestations (Image Series) - Figure 9 (Image Series) - Recurrent Genital Herpes: Manifestations
Image 9A: Recurrent Genital HSV Lesions—Vesicle Phase

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

Source: University of Washington Virology Research Clinic



Figure 9 (Image Series) - Recurrent Genital Herpes: Manifestations
Image 9B: 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 9 (Image Series) - Recurrent Genital Herpes: Manifestations
Image 9C: Recurrent Genital HSV—Wet Ulcer Phase

Left labial ulcerative lesion in woman with recurrent HSV.

Source: University of Washington Virology Research Clinic

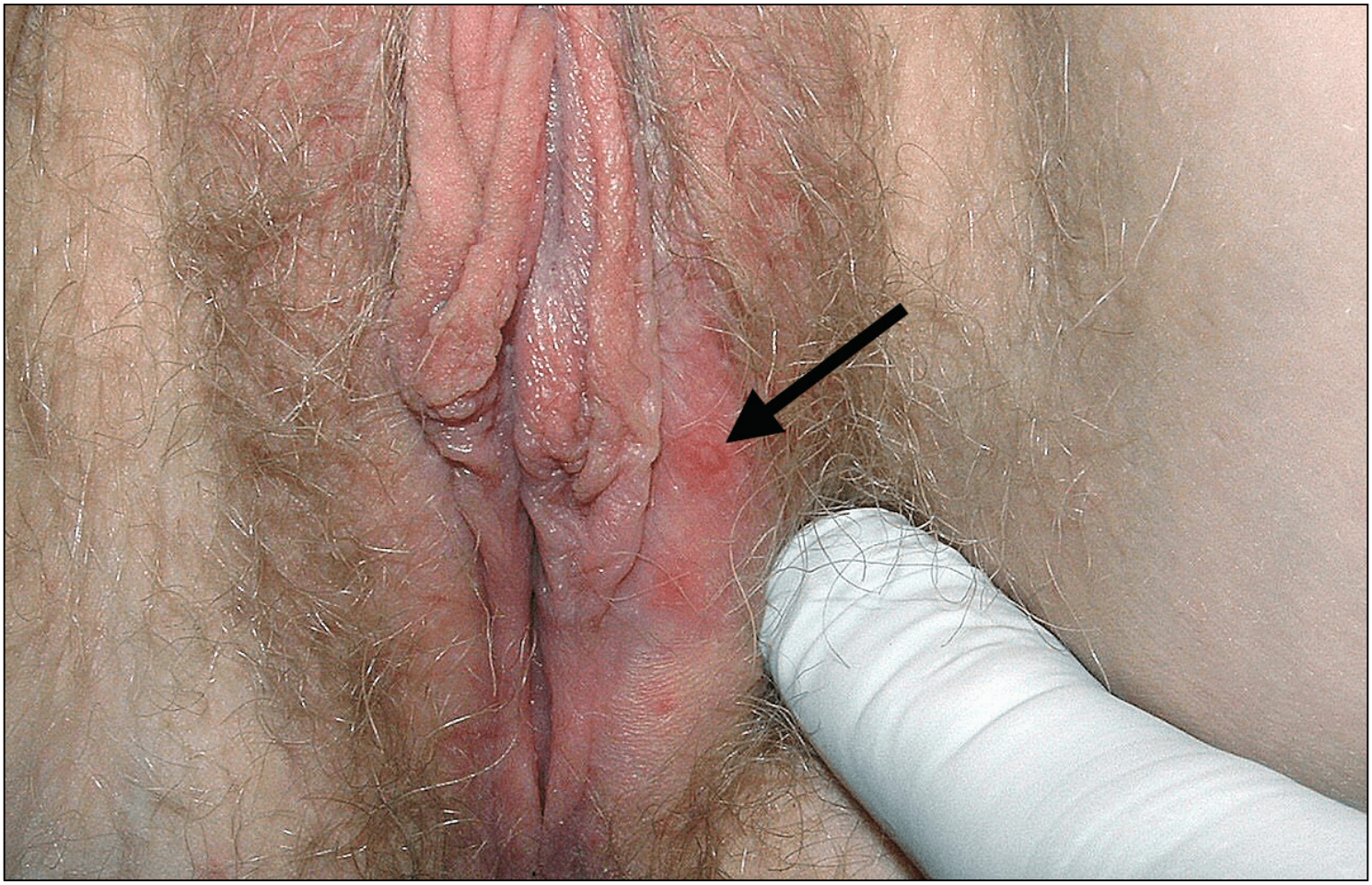


Figure 9 (Image Series) - Recurrent Genital Herpes: Manifestations
Image 9D: Recurrent Genital Herpes—Dry Crusted Phase

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 9 (Image Series) - Recurrent Genital Herpes: Manifestations
Image 9E: Recurrent Genital HSV Lesion—Dry Crusting Phase

This individual with recurrent genital herpes presented with a history of several days 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 polymerase chain reaction (PCR). At the time the patient presented for evaluation, the HSV lesion was in the dry crusting phase.

Source: Negusse Ocbamichael, King County Public Health Sexual Health Clinic



Figure 10 Recurrent Genital HSV Manifested as Asymptomatic Fissure

This photograph shows an asymptomatic HSV lesion manifested as a small linear fissure on right inner labia (arrow).

Source: University of Washington Virology Research Clinic

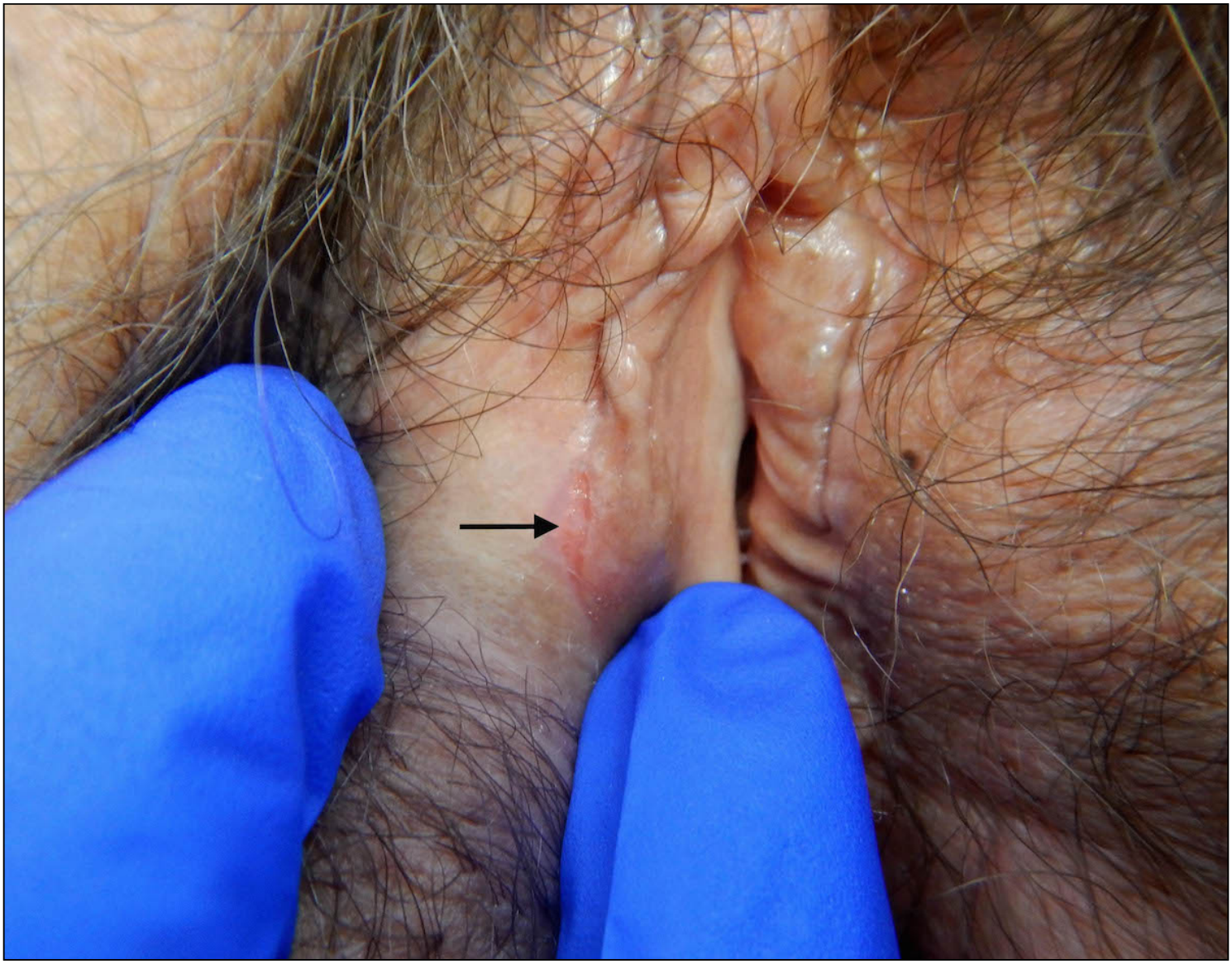


Figure 11 Acyclovir Mechanism of Action

After acyclovir enters a cell infected with HSV, it is initially activated by viral thymidine kinase (TK); the second and third phosphorylation steps occur through cellular kinases. The active drug acyclovir triphosphate then inhibits HSV DNA replication.
Abbreviations: HSV = herpes simplex virus; TK = thymidine kinase; ACV = acyclovir; P = phosphate

Illustration by David H. Spach, MD

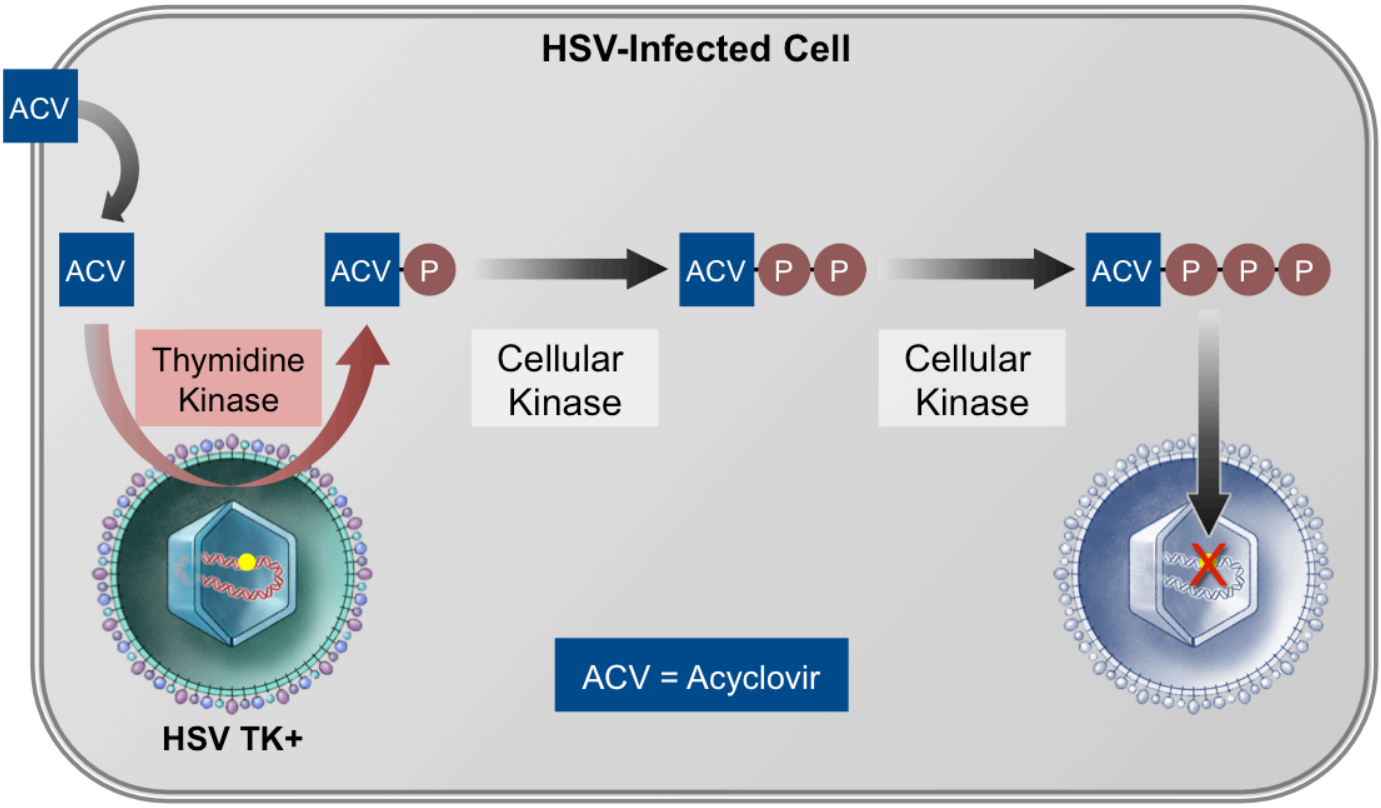


Figure 12 Acyclovir-Resistant HSV

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.
Abbreviations: HSV = herpes simplex virus; TK = thymidine kinase; ACV = acyclovir; P = phosphate.

Illustration by David H. Spach, MD

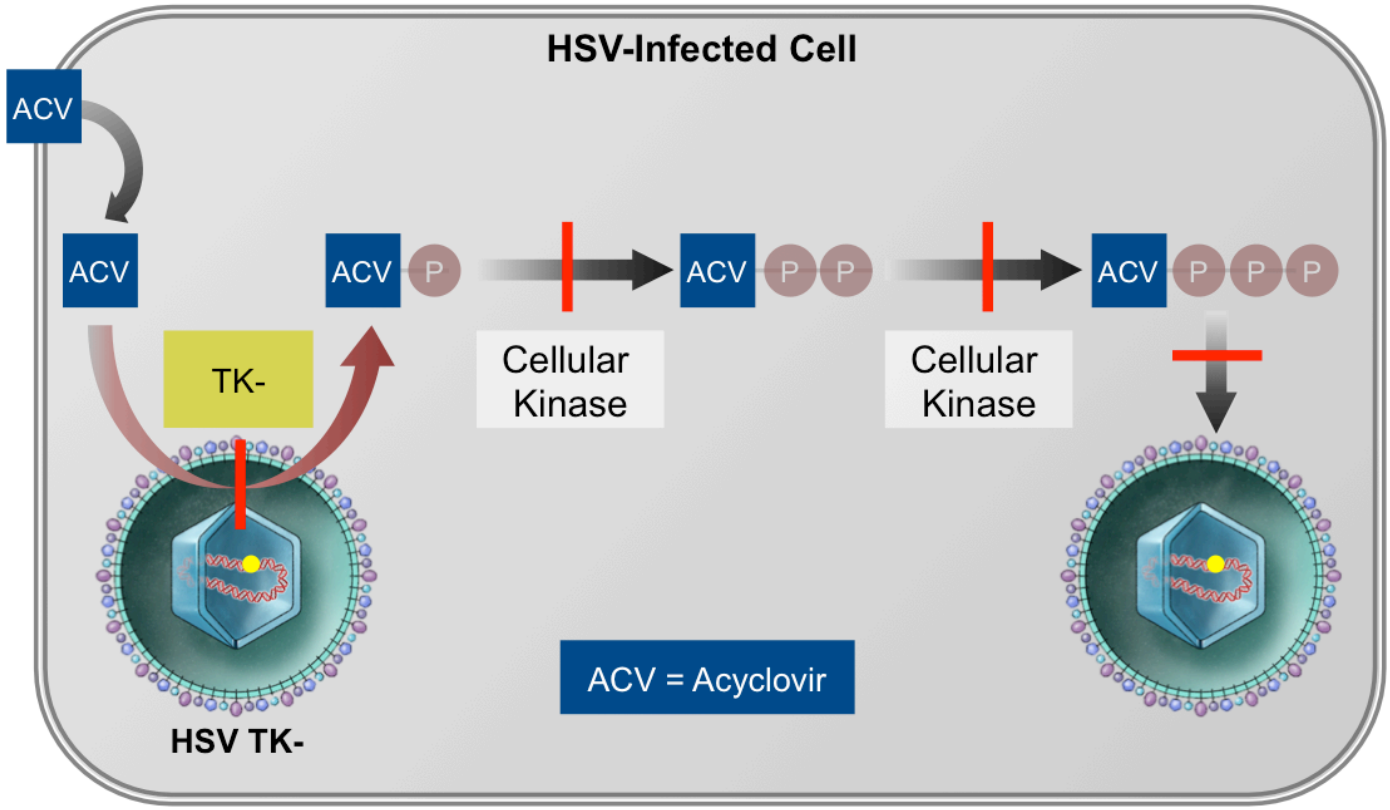


Figure 13 Primary Oral HSV Infection

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

Source: University of Washington Virology Research Clinic



Figure 14 Valacyclovir to Reduce Transmission of Genital HSV

This study involved 1,484 HSV-serodiscordant, heterosexual, monogamous couples. Partners with symptomatic genital HSV-2 infection received 8 months of oral valacyclovir 500 mg once daily or placebo.

Source: Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11-20.

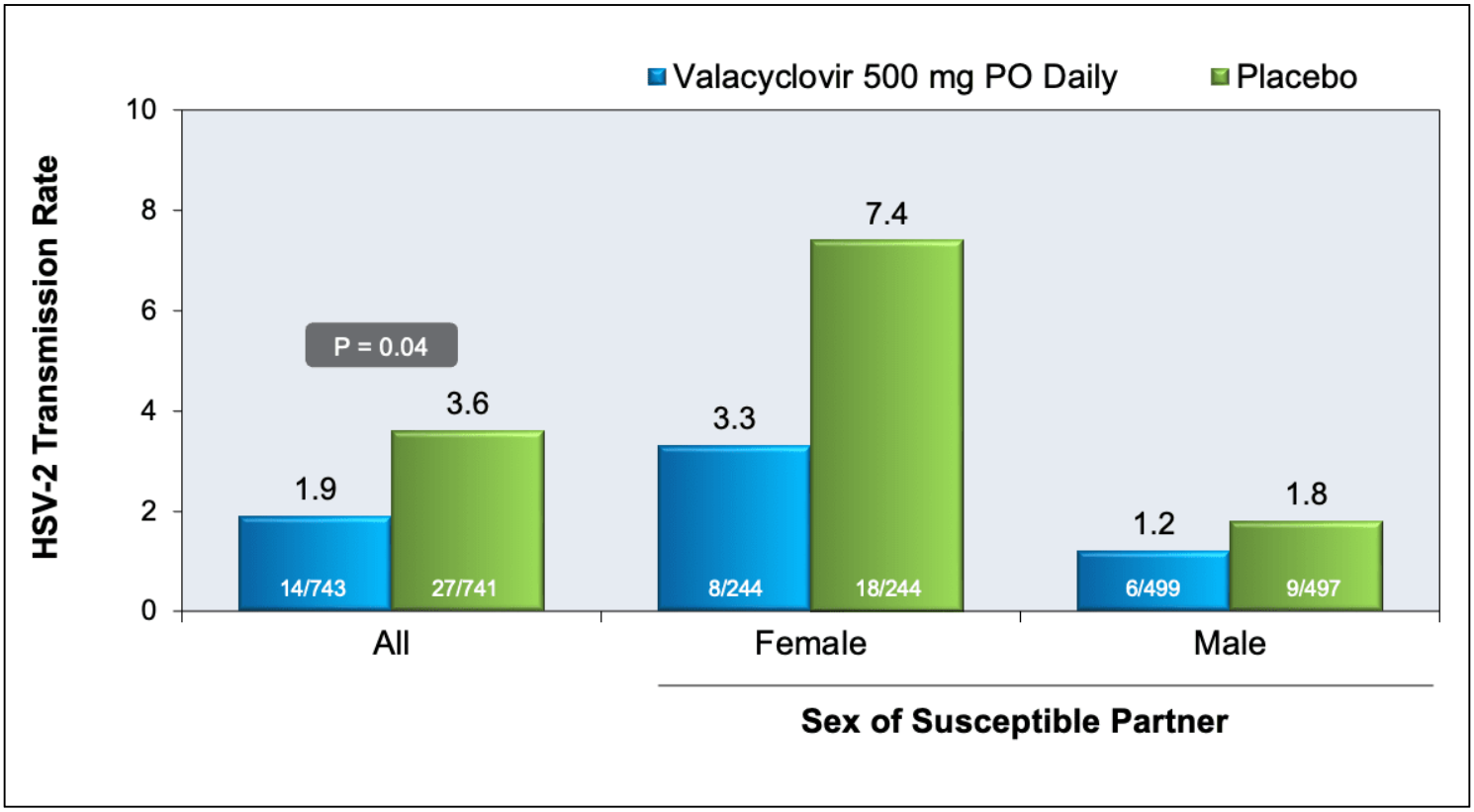


Table 1. 2021 STI Treatment Guidelines: Genital Herpes
Treatment of First Clinical Episode of Genital Herpes

For all recommended regimens, note that treatment can be extended if healing is incomplete after 10 days of therapy.

Recommended Regimens
Acyclovir *400 mg orally three times a day for 7–10 days*

Recommended Regimens
Famciclovir *250 mg orally three times a day for 7–10 days*

Recommended Regimens
Valacyclovir *1 g orally twice a day for 7–10 days*

Acyclovir 200 mg orally five times/day is also effective but is not recommended because of the frequency of dosing.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 2. 2021 STI Treatment Guidelines: Genital Herpes
Episodic Therapy for Recurrent HSV-2 Genital Herpes

Recommended Regimens
Acyclovir *800 mg orally twice a day for 5 days*

Recommended Regimens
Acyclovir *800 mg orally three times a day for 2 days*

Recommended Regimens
Famciclovir *1 g orally twice daily for 1 day*

Recommended Regimens
Famciclovir *500 mg orally once, followed by 250 mg orally twice daily for 2 days*

Recommended Regimens
Famciclovir *125 mg orally twice daily for 5 days*

Recommended Regimens
Valacyclovir *500 mg orally twice a day for 3 days*

Recommended Regimens
Valacyclovir *1 g orally once a day for 5 days*

Acyclovir 400 mg orally 3 times/day is also effective, but is not recommended because of frequency of dosing.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 3. 2021 STI Treatment Guidelines: Genital Herpes
Suppressive Therapy for Recurrent HSV-2 Genital Herpes

Recommended Regimens
Acyclovir *400 mg orally twice a day*

Recommended Regimens
Valacyclovir *500 mg orally once a day*
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).

Recommended Regimens
Valacyclovir *1 g orally once a day*

Recommended Regimens
Famciclovir *250 mg orally twice a day*

Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because the frequency of genital HSV-2 recurrence diminishes over time for many persons.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 4. 2021 STI Treatment Guidelines: Genital Herpes
Episodic Therapy for Recurrent Genital Herpes Among Persons with HIV*

Recommended Regimens
Acyclovir *400 mg orally three times a day for 5–10 days*

Recommended Regimens
Famciclovir *500 mg orally twice a day for 5–10 days*

Recommended Regimens
Valacyclovir *1 g orally twice a day for 5–10 days*

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

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 5. 2021 STI Treatment Guidelines: Genital Herpes Daily Suppressive Therapy Among Persons with HIV

Recommended Regimens
Acyclovir *400–800 mg orally two to three times a day*

Recommended Regimens
Famciclovir *500 mg orally twice a day*

Recommended Regimens
Valacyclovir *500 mg orally twice a day*

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 6. 2021 STI Treatment Guidelines: Genital Herpes Suppression of Recurrent Genital Herpes Among Pregnant Women*

*Treatment recommended starting at 36 weeks of gestation

Recommended Regimens
Acyclovir *400 mg orally three times a day*

Recommended Regimens
Valacyclovir *500 mg orally twice a day*

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 7. 2021 STI Treatment Guidelines: Genital Herpes
Treatment of Neonatal Herpes

Recommended Regimen for Infants with Neonatal Herpes Limited to the Skin and Mucous Membranes
Acyclovir *20 mg/kg body weight IV every 8 hours for 14 days*

Recommended Regimen for Infants with Neonatal Herpes who have Disseminated Disease and Disease Involving the Central Nervous System
Acyclovir *20 mg/kg body weight IV every 8 hours for 21 days*

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Diseases characterized by genital, anal, or perianal ulcers: genital herpes. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]