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New Concepts in Understanding Genital Herpes

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Abstract

Herpes Simplex Virus-2 (HSV-2) is a lifelong infection that causes recurrent genital ulcers and on rare occasions, disseminated and visceral disease. Herpes simplex virus-1 (HSV-1) infection is an increasingly important cause of genital ulcers as well. Herpes simplex virus (HSV) infections are the most common cause of genital ulcers in adults but acquisition and chronic infection are more commonly asymptomatic than symptomatic. Both the symptomatic and asymptomatic forms of HSV are of clinical consequence for several reasons. HSV-2 infection enhances HIV-1 acquisition, as well as transmission. In addition, both sexual and perinatal transmission can occur during asymptomatic viral shedding. Perinatal transmission is of particular concern because neonatal HSV infection results in severe morbiditiy to the newborn. Antiviral medicines are effective for limiting recurrence duration and decreasing transmission likelihood, though no available intervention completely prevents transmission. This highlights the importance of laboratory diagnostics for this lifelong infection, as well as the need for an HSV vaccine.

Herpes simplex virus-2 (HSV-2) is the most common cause of genital ulcers, but can replicate in all human tissue and occasionally causes keratitis, hepatitis, pneumonitis, meningitis and neonatal sepsis. Seroprevalence is high worldwide and is 17% in the United States [1]. Though the predominant feature of HSV-2 infection is crops of painful lesions, most seropositive patients are asymptomatic and unaware of their diagnosis [2,3]. In symptomatic and asymptomatic persons, infection is characterized by frequent asymptomatic genital tract shedding [3–5], which promotes transmission [6], and persistent inflammation [7]. Immune cell infiltration may explain enhanced human immunodeficiency virus-1 (HIV-1) acquisition [8] and HIV-1 transmission [9] in HSV-2 infected persons. Short courses of DNA nucleoside analogues limit duration of primary infection [10] and recurrences [11], and prevent 50% of transmissions within discordant couples [12]. Because condoms [13,14] and education are only partially effective in preventing transmission, an HSV-2 vaccine is a public health priority.

Epidemiology

HSV-2 infection is widely dispersed among populations worldwide [15]. HSV-2 is usually spread via sexual contact and appearance of HSV-2 antibodies in a population correlates with initiation of sexual activity during puberty. HSV-1 is an increasingly important cause of genital ulcer disease in the developed world [1,16]. In much of Asia and Africa, the majority of adults have HSV-1 antibodies and infection is typically acquired during childhood. Since World War II, childhood HSV-1 acquisition has decreased during childhood in certain Western populations. A recent consequence is an upsurge in sexually acquired HSV-1 infections in

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adolescents via oro-genital transmission, and an increased proportion of neonatal HSV cases due to HSV-1 [16].

Serologic testing allows for detailed characterization of HSV-2 infection worldwide. HSV-2 prevalence is high in sub-Saharan Africa and generally lower in Europe, Australia, Latin America and Asia. Prevalence varies locally according to the risk group being surveyed. In the United States, seroprevalence decreased from 22% in 1991 to 17% in 2004 [1]. However, a more detailed analysis reveals important secular trends. Cumulative lifetime incidence is 25% among white women, 20% among white men, 80% among black women and 60% among black men. In virtually all cohorts, women have higher HSV-2 prevalence than men, though men who have sex with men are also at high risk. There is an age cohort effect for all subgroups because likelihood of infectious exposure to HSV increases over the course of a lifetime. Increased HSV-2 prevalence is associated with lifetime number of sexual partnerships, lower age of sexual debut, and a history of other sexually transmitted infections [17].

Recent clinical trials and cohort studies studying condoms as a means of HSV prevention allowed for accrual of incidence rather than just prevalence data for HSV infection [2,14]: these studies provide important new information for selection of study cohorts for clinical trials, and for selection of populations for public health interventions. Incidence data is difficult to measure because most seroconversions are asymptomatic [2], and new lesions may be located in non-visible locations such as the rectum in men who have sex with men.

Seroincidence reflects both the risk of the studied population as well as the underlying seroprevalence. For example, incidence was much higher in an urban youth cohort (11.7 cases per 100-person years) entering sexual debut [18], than in an older cohort of men who have sex with men (1.9 cases per 100-person years) with a high baseline HSV-2 prevalence of 20% [19]. In most studies, acquisition rates are higher among women than men, and higher among HIV-1 positive than HIV-1 negative participants. Prior HSV-1 infection does not appear to decrease incidence of HSV-2 infection, though sub-clinical HSV-2 acquisition is three times as likely in HSV-1 positive persons [2].

A critical difference between HSV-2 and bacterial sexually transmitted diseases is that HSV-2 is often transmitted within long-term couples rather than in high-risk core groups, and likely sustains high seroprevalence within a population via this mechanism. The median time to transmission within discordant couples is 3 months with a median number of 24 sexual acts prior to transmission [14]. Longitudinal studies of serodiscordant couples reveal annual seroconversion rates of 3% to 12% among negative partners [12,14,20]. Therefore, physicians should target serodiscordant couples for interventions that decrease the likelihood of transmission.

HSV-2 Transmission and Asymptomatic Shedding

Transmission of HSV occurs when a person who is shedding virus in the genital tract or on other skin or mucosal surface, inoculates virus onto a mucosal surface or small crack in the skin of a sexual partner. A key determinant of transmission is the nature of HSV-2 shedding in the source partner. Over the last decade, the concept of subclinical shedding in the genital tract has taken on increasing importance. Initial protocols indicated that approximately one third of HSV-2 shedding episodes occur in the absence of genital lesions or symptoms[5]. More recent studies employing swabs every six hours suggest that over 75% of mucosal HSV-2 reactivations are subclinical, with half of episodes lasting less than 12 hours. Ninety-three percent of reactivations lasting less than 24 hours are without clinical symptoms [4]. A key component in defining the nature of subclinical shedding of HSV-2 is the use of quantitative PCR which has increased sensitivity compared to culture for presence of HSV in the genital

tract [21]. Transmission in the absence of a positive culture has been documented, and most sexual and maternal-fetal transmissions occur during episodes of subclinical shedding [6,22].

In comparison to symptomatic HSV-2 shedding episodes, asymptomatic episodes tend to be shorter duration (we have documented episodes lasting two hours), and have lower peak HSV copy number [4]. Sites of subclinical shedding include the cervix, vulva, anus, urethra, penile skin and peri-anal region [4], and concomitant shedding can occur at several anatomic sites. For these reasons, patients with genital herpes should be educated about potential for infectivity regardless of symptomatology.

Pathogenesis

During primary infection, replication of virus is initiated in the nucleated cells of the dermis and epidermis. Each infected cell is inevitably killed and the number of involved cells in part determines whether a clinical lesion develops, or whether as is commonly the case, primary infection is subclinical. Under both circumstances, sensory nerve endings become infected, virus is transported via the axon to the sacral ganglia, and latency is established [23]. HSV can only be cultured from the ganglia during primary infection. Virus is spread to other sites where vesicles ultimately form via centrifugal migration of HSV-2 to other sensory nerves, and via autoinoculation. Viremia occurs in ~25% of patients with primary infection [24].

HSV-2 maintains itself in a down-regulated latent state in the ganglia where immune activation is limited. Autopsy studies reveal that approximately 2% to 11% of neurons harbor virus [23]. Experimental data suggest that reactivation in the ganglia leading to release of virus in the genital tract is limited by T lymphocyte and cytokine signaling within the ganglia [25]. However, mathematical models predict that reactivation occurs more frequently than detection of virus in the genital tract, which is present on average 20% (range 0% to 78%) of the time [26]. This implies loose control of viral release at the ganglia, which is a surprising new concept in the field of HSV-2 pathogenesis.

Viral release from sensory neurons into the genital tract leads to either subclinical shedding of virus, or development of a herpetic genital lesion. Host immune responses, especially CD8+ lymphocyte expansion, appear to be critical determinants in the clearance of a genital lesion [27]. Herpetic ulcers are accompanied by dense CD8+infiltration as well as by large numbers of CD4+ lymphocytes and dendritic cells [28]. The clinical importance of these responses is highlighted in certain immunocompetent hosts who develop either high frequency of shedding or persistent, poorly healing genital lesions.

Clinical Presentation

Primary infection

Clinical presentation and course of initial HSV infection depends on many factors including anatomic site, age and immune status of the host, antigenic type of the virus, sites of viral replication, and probably initial viral titer of the infectious inoculum. *Primary infection* is defined as first infection with either HSV-1 or HSV-2 in which the host lacks HSV antibodies in acute-phase serum. There is an important distinction between *true primary infection* (acquisition of HSV-1 or 2 in the HSV seronegative person) and *first documented infection* because patients sometimes first notice genital lesions well after primary infection and seroconversion. About 25% of patients with first episode genital herpes already have evidence of a full complement of HSV-2 antibodies, implying acquisition in the past [29].

Primary genital herpes is asymptomatic approximately half of the time even when close monitoring for clinical symptoms is present [2]. Symptomatic disease is associated with

prolonged duration of symptoms, lesions (10 – 12 days), and viral shedding. First episode genital herpes is commonly associated with fever, headache, malaise and myalgias. Pain, itching, dysuria, tender inguinal lymphadenopathy and a clear mucoid discharge are predominant local symptoms that characteristically peak at approximately one week in the absence of therapy. Lesions progress through various stages. A typical lesion starts as a vesicle, converts to a pustule and then to a painful ulcer, which ultimately crusts and finally heals without a scar. Lesions are often multiple, widely spaced, and are often in various stages of development. Lesions during primary infection can coalesce and are present for an average of 20 days in women and 17 days in men [30].

Certain sites of primary infection warrant special mention. Primary HSV cervicitis can be confused with *Chlamydia trachomatis* and *Neisseria gonorrhea* infection. Helpful distinguishing features are dysuria out of proportion to the limited inflammation typically seen on urinalysis, and cervical ulceration, rather than diffuse inflammation, on physical exam. HSV proctitis is often associated with rectal intercourse while peri-anal herpetic lesions can be seen in heterosexual men and women who report no anal intercourse. Proctitis is characterized by tenesmus, anorectal discharge, pain, constipation, and ulceration and necrosis on sigmoidoscopy [31].

Primary genital HSV-1 and HSV-2 infections are identical in their presentations. Primary HSV-2 in persons with an HSV-1 antibody is associated with decreased likelihood of systemic symptoms such as fever, and more rapid lesion healing.

Reactivation and recurrence

Ninety percent of persons with primary HSV-2 recur during the first year of infection [32], and virtually all newly infected persons shed HSV-2 subclinically. There is great variability in frequency of recurrence: 20% of patients recur more than ten times during the first year while the median number of recurrences is four to five. In general, recurrences decrease over a five-year period, but in some patients increase in frequency. HSV-1 recurs less commonly in the genital tract than HSV-2 following primary genital infection [33].

Recurrence is typically milder and less prolonged than primary infection with itching and pain confined to a single, relatively small mucocutaneous site. A typical prodrome, consisting of tingling at the lesion site and shooting pains in the buttocks and hips 0.5 to 48 hours prior to a lesion, is often the most bothersome feature [30]. The appearance of recurrent herpetic lesions is diverse. Even experienced clinicians can misdiagnose “atypical” linear or serpiginous collections of multiple round vesicles and ulcers: the positive and negative predictive value of physical examination alone is poor for diagnosis of genital herpes [2]. In addition, about half of patients who previously do not recognize herpetic lesions and were unaware that they had HSV-2, learn to observe recurrent lesions and symptoms after education sessions [3].

Extra-genital infections / local complications

During primary infection, extragenital lesions often occur two weeks after primary infection on the finger, buttock, groins or thigh. The cause of this is likely to be direct extension of virus. Herpetic whitlow presents as a vesicle or pustule on the finger-tip associated with profound pain and regional adenopathy. Therapy is with antiviral chemotherapy and surgery is contraindicated to avoid further infectious spread. Infection often recurs in the same finger. Herpes gladiatorum occurs among wrestlers and involves virtually any area of the skin, particularly on the face and chest.

Aseptic meningitis presents with fever, headache, photophobia and nuchal rigidity and is extremely common during primary infection, particularly in women (approximately 1/3 of

primary infections). Lumbar puncture reveals a lymphocyte predominance and elevated protein level. HSV PCR should be sent for definitive diagnosis. HSV-2 is the also the most common cause of recurrent lymphocytic meningitis: these recurrences can occur concordant with or independent from genital lesions [34].

HSV encephalitis is an extremely serious infection that is usually caused by HSV-1 and as such has less of a correlation with genital herpes. It should be suspected when fever is accompanied by acute onset alteration in mental status. HSV keratitis is similarly caused by HSV-1 in the majority of cases but is the most common cause of corneal blindness in the United States. Chorioretinitis is a devastating condition that leads to acute painless vision less that is bilateral in ¼ of cases, and is diagnosed by characteristic ophthalmologic examination with vitreal tap for HSV PCR. Pregnant women and immunocompromised hosts are affected, though infection is not exclusive to these hosts [35].

Occasionally, disseminated HSV occurs and can involve the liver, or lungs. Pneumonitis usually occurs in severely immuncompromised hosts and leads to focal necrosis of the lungs. HSV rarely causes severe hepatitis both in immunocompetent and immunocompromised hosts. Esophagitis most commonly occurs in AIDS patients and should be differentiated from CMV and *Candida* infections.

Diagnosis

When characteristic multiple vesicular lesions appear on an erythematous base in a sexually active adult or adolescent, a clinical diagnosis can be inferred and therapy can be started empirically to limit the prolonged, severe symptoms of first episode genital herpes. However, clinical exam is notoriously insensitive and non-specific for diagnosis of genital herpes [36]. Because herpes is a lifelong infection with ramifications for health, relationships and pregnancy, a laboratory diagnosis is essential.

During lesions, HSV is best confirmed by isolation of virus in tissue culture or demonstration of HSV DNA using PCR from lesion scrapings. Sensitivity of PCR is significantly higher (2- to 4-fold) than for culture [21]. Culture sensitivity can be maximized by sampling vesicle fluid rather than an ulcer base, and is higher during primary infection. If diagnosis is needed when a lesion is not present, or if HSV is not isolated from a genital lesion, then type-specific serology is useful, particularly in patients with longstanding infection. The Western Blot assay is the gold standard for antibody diagnosis and carries a sensitivity and specificity greater than 98% [37]. Whole viral extract assays are prone to high likelihood of false positive and negative tests and are to be avoided. Viral isolation, HSV DNA PCR, serology, and Western Blot all permit viral sub-typing, which in turn provides critical prognostic information for the clinician and patient.

Treatment

For genital herpes and visceral HSV infections, the DNA nucleoside analogues, including acyclovir, famciclovir and valacyclovir are the mainstays of therapy. While acyclovir and its related compounds have a limited side effect profile, intravenous acyclovir can lead to crystallization in the renal outflow tract though this can be largely avoided with adequate hydration. Intravenous therapy is warranted for visceral disease, neonatal herpes and encephalitis [38].

Drug resistant HSV is largely limited to the immunocompromised host and can be treated with foscarnet or cidofovir. Foscarnet commonly causes renal insufficieny, elctrolyte wasting and nausea [39]. Cidofovir is dosed weekly, is also nephrotoxic, commonly causes rash and chills,

and needs to be dosed with probenecid. Patients also need to be monitored for leucopenia [40].

DNA nucleoside analogues have proven efficacy in limiting the duration of first-episode genital herpes infection, and in limiting the duration and severity of recurrences. It is now recognized that short course therapy is often a conveneient and inexpensive option for recurrences in immuncompetent patients (Table 1). The DNA nucleoside analogues can be taken prophylactically on a daily basis to limit recurrence frequency, asymptomatic shedding, and to decrease HSV-2 transmission between serodiscordant monogamous couples (Table 1) [38].

Prevention

HSV-2 shedding persists for decades after primary infection. Therefore, a key component in the care of HSV-2 infected persons is counseling regarding prevention of transmission. Full disclosure to sexual partners [41], along with abstinence during genital lesions, and condom use [13,14], are proven to decrease though not eliminate transmission. In addition, Valacyclovir 500 mg daily given to the source partner reduces transmission probability by about 50% [12]. Development of an effective HSV vaccine is the best potential approach for prevention but to date no licensed vaccine is available. An HSV-2 gD2 protein given with an adjuvant showed efficacy only in a subgroup of patients: women who were negative for HSV-1 [20]. This product is being more extensively studied in this population but will have limited use globally. In addition, a widely efficacious vaccine will have a very gradual effect on HSV-2 prevalence given the chronic nature of the disease. Therefore, the behavioral interventions and antiviral prophylaxis described above will likely be necessary for years to come.

HSV and Pregnancy

Clinical manifestations of chronic genital herpes infection are similar in pregnant and non-pregnant women, though pregnancy does increase the frequency of recurrence. Primary infection during pregnancy is more commonly associated with complications such as visceral dissemination, particularly if infection is acquired during the third trimester[42]. Therefore, most authorities recommend that primary infection during pregnancy should be treated with systemic antiviral medications.

Neonatal HSV infection is a devastating infection characterized by dissemination and a 65% mortality rate and 80% rate of long-term disability, even with antiviral therapy. Cutaneous lesions are common but often occur well into disease progression and lack of skin findings has no negative predictive role for neonatal HSV [43]. Congenital infection is rare and occurs usually during primary infection of the mother during third trimester: microcephaly and chorioretinitis are common features. Treatment for visceral disease is with high-dose intravenous acyclovir (20 mg/kg every eight hours for 21 days) [38].

Most transmission to the neonate occurs during delivery, while many fewer cases are due to post-natal contact. The highest risk for transmission of HSV during the peri-natal period occurs when HSV is acquired late during the third trimester. The likelihood of transmission due to recurrence of chronic HSV-2 is much lower. However, because HSV2 infection is so widespread (22% of all pregnant women), the majority of transmissions in the United States occur via this mechanism [22,44].

The high HSV-2 prevalence and low incidence of neonatal disease (1 per 6000 – 20000 live births) indicate that only a relatively low number of neonates are at risk for acquiring HSV [45]. Preventative approaches should focus on avoidance of infant contact with active HSV lesions. After a delivery of an infant from a mother with active lesions, the infant should be

placed in isolation and viral cultures, liver function studies and CSF examination should be obtained. Physicians should closely observe these infants, and respond to any evidence of neonatal disease with empiric treatment and a repeat diagnostic work up.

Infants born by cesarean section to prior to rupture of membranes are at minimal risk for developing neonatal HSV infection. Therefore, this intervention is appropriate if genital lesions are detected on physical examination, or in women with first-episode genital herpes during third trimester. We advocate for abdominal delivery in the presence of genital lesions even if rupture of membranes has occurred. The frequency of transmission is markedly higher from women who acquire HSV near term (30% – 50%) than among those who reactivate at delivery (<1%): a substantial effort should be made to identify this group of women via history [22]. The presence of HSV by PCR or viral isolation in the absence of HSV-2 antibody confirms this diagnosis. Primary HSV-1 is associated with a particularly high likelihood of transmission [46]. Therefore, oro-genital sexual contact should be discouraged during the third trimester in women with no history of oral herpes.

Because transmission may occur during asymptomatic shedding, current protocols are evaluating whether rapid PCR of genital swabs of the vagina and cervix during labor can be used to determine the need for abdominal delivery as well as identify infants at high risk of neonatal HSV. While logical, the ability of this approach to reduce neonatal HSV is unknown. For now, women without visible lesions should undergo vaginal delivery, though the presence of shedding will provide important information for the pediatrician if the infant develops fever or other signs of infection after delivery. There is no role for weekly surveillance for HSV with genital swabs during pregnancy, or for amniocentesis.

HSV-2 and Human Immunodeficieny Virus-1 Infection

The epidemiology of HSV-2 infection is tightly linked to that of HIV-1 infection. The two infections are chronic viral infections that are most commonly spread via the same mechanism, sexual contact. Moreover, both infections have made significant inroads into populations outside of traditional core groups, particularly in sub-Saharan Africa [47]. This occurred via spread through complex sexual networks where traditional measures of risk are less predictive. For instance, a high percentage of new HSV-2 and HIV-1 infections occur among HIV-1 seronegative members of discordant couples who are linked to a high-risk network due to the sexual activity of their partner rather than their own sexual activity [48]. HIV-1 was generally introduced into populations after HSV-2 such that HSV-2 delineated paths of transmission for HIV-1 at the onset of epidemics driven by sexual spread. As a result, HSV-2 infection is particularly common among HIV-1 infected persons including men who have sex with men, and HIV-1 positive persons within serodiscordant couples.

In addition, HSV-2 probably augmented the spread of HIV-1 via separate biologic mechanisms. Current studies suggest that HSV-2 seropositivity increases risk of HIV-1 acquisition threefold [8]. Source partner plasma HIV-1 viral load and susceptible partner HSV-2 serostatus increase per-contact probability of HIV-1 equally [9]. HSV-2 infection induces infiltration of CCR5+ CD4+ lymphocytes into the genital tract: recent studies indicate that these cells persist for several months after healing of a genital lesion and that *ex vivo* infection of genital skin from herpetic lesions supports HIV-1 replication at much higher levels than genital skin from non-herpetic areas [7,28]. There is therefore a reasonable biological mechanism to explain enhanced HIV-1 acquisition. Thus the prolonged subclinical persistence of HIV receptor positive cells in the genital tract provides a biological mechanism to explain enhanced HIV-1 acquisition in HSV-2 infected persons. Unfortunately antiviral therapy with acyclovir does not alter these processes [28].

Sexual and maternal to fetal transmission of HIV-1 appears to occur more efficiently from persons co-infected with HSV-2 [49]. During and for several weeks after reactivation of herpetic lesions, plasma HIV-1 viral load increases [50], which is critical because plasma HIV-1 viral load is a key factor of transmissibility. Twice daily valacyclovir lowers HIV-1 plasma viral load by 0.5 log10 and decreases the frequency and mean quantity of HIV-1 shed in the genital tracts[51].

Based on these assumptions, it is estimated that approximately one quarter of all HIV-1 infections in certain settings in sub-Saharan Africa may be attributable to HSV-2 infection [47]. Unfortunately, two large randomized controlled trials showed no decrease in HIV-1 acquisition when acyclovir was given twice daily to HSV-2 seropositive women in Africa and MSM in Peru and the United States [52,53]. In addition, a randomized controlled trial among HIV-1 serodiscordant couples in Africa, in which the HIV-1 and HSV-2 infected partner received Acyclovir, showed no decrease in HIV-1 transmission to the seronegative partner (A. Wald personal communication).

Though these clinical trial results are disappointing, they do not imply rejection of these concepts. HSV-2 shedding persists at lower levels in patients treated with nucleoside analogues. In addition, intense lymphocyte infiltration remains despite therapy and may serve as targets for primary HIV-1 infection [28]. Potential issues may therefore be inadequate dosing regimens given the pharmacokinetic properties of current agents. In the transmission trial, the issue may be that HIV-1 viral load was not decreased enough to make a difference in transmission risk. It was originally hypothesized that acyclovir lowers HIV-1 plasma viral load via an indirect mechanism of lowering HSV-2 associated inflammation. More recent data suggest that acyclovir may have direct anti-HIV-1 effects as a reverse transcriptase inhibitor *in vitro* and can even induce experimental mutations that lead to drug resistance among HIV-1 isolates. The levels used for such studies are not attainable in human clinical studies [54,55]. Therefore, the actual direct effect of acyclovir on HIV-1 *in vivo* is less clear. This is another area of intense current research.

Conclusion

HSV-2 remains an important pathogen that is widespread in numerous populations, and occasionally causes severe infections particularly in neonates and immunocompromised hosts. Current areas of intense interest are development of antiviral agents that completely suppress recurrences, viral shedding, sexual transmission, and neonatal transmission, as well as development of a vaccine. These interventions may in turn be of relevance to future HIV-1 prevention programs given the synergy of these two chronic viral pathogens.

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Table 1

CDC recommended treatment regimens for genital herpes [38].

First episode*
• Acyclovir 400 mg orally three times a day for 7 – 10 days
• Acyclovir 200 mg orally five times a day for 7 – 10 days
• Famciclovir 250 mg orally three times a day for 7 – 10 days
• Valacyclovir 1 g orally twice a day for 7 – 10 days
Suppressive therapy for recurrent genital herpes
• Acyclovir 400 mg orally twice a day
• Famciclovir 250 mg orally twice a day
• Valacyclovir 1 g orally daily
• Valacyclovir 500 mg orally daily
Episodic therapy for recurrent genital herpes
• Acyclovir 400 mg orally three times a day for 5 days
• Acyclovir 800 mg orally two times a day for 5 days
• Acyclovir 800 mg orally three times a day for 2 days
• Famciclovir 125 mg orally two times a day for 5 days
• Famciclovir 1 g orally two times a day for 1 day
• Valacyclovir 500 mg orally twice a day for 3 days
• Valacyclovir 1000 mg orally daily for 5 days
Suppressive therapy for recurrent genital herpes in HIV infected patients
• Acyclovir 400–800 mg orally twice or three times a day
• Famciclovir 500 mg orally twice a day
• Valacyclovir 500 mg orally twice daily
Episodic therapy for recurrent genital herpes in HIV infected patients
• Acyclovir 400 mg orally three times a day for 5–10 days
• Famciclovir 500 mg orally twice a day for 5–10 days
• Valacyclovir 1 g orally twice daily for 5–10 days

*Extension of therapy beyond ten days is appropriate if lesions healing has yet to occur.