Actas Dermosifiliogr. 2009;100:22-32

ADVANCES IN DERMATOLOGY

Update on the Treatment of Genital Herpes

J.M. Martín, G. Villalón, and E. Jordá
Servicio de Dermatología, Hospital Clínico Universitario, Valencia, Spain..

Abstract. Genital herpes is a chronic infection characterized by periodic reactivation. It can produce symptomatic disease in the host although asymptomatic viral excretion can also occur. It is currently the main cause of genital ulceration and an important public health problem that has substantial clinical, psychological, and economic repercussions. This review analyzes the currently available therapeutic options and regimens, which are based mainly on systemic use of antiviral agents such as aciclovir, valacyclovir, and famciclovir. In addition, special emphasis is placed on the prevention and management of this infection in specific situations, such as pregnant, pediatric, and immunocompromised patients.

Key words: genital herpes, sexually transmitted disease, aciclovir, valac

ACTUALIZACIÓN EN EL TRATAMIENTO DEL HERPES GENITAL

Resumen. El herpes genital es una infección crónica que se caracteriza por una reactivación periódica, con capacidad tanto de producir una enfermedad sintomática en el huésped como de excreción viral asintomática. Hoy en día constituye la primera causa de ulceración genital y representa un importante problema de salud pública, con considerables repercusiones clínicas, psicológicas y económicas.
Se revisan y actualizan las distintas opciones y pautas terapéuticas disponibles en la actualidad, basadas fundamentalmente en el empleo por vía sistémica de los fármacos antivirales aciclovir, valaciclovir y famciclovir. Por otro lado, se pone especial énfasis en la prevención y el manejo de esta infección en situaciones particulares, como en embarazadas, en niños, o en pacientes inmunodeprimidos.

Palabras clave: herpes genital, enfermedades de transmisión sexual, aciclovir, valaciclovir, famciclovir.

Introduction, Background, and Epidemiology

Genital herpes is one of the most widely distributed sexually transmitted diseases throughout the world and is the main cause of genital ulceration.

It is currently an important public health problem that has considerable physical, psychological, and economic repercussions and also increases the risk of transmission of the human immunodeficiency virus (HIV).[1]

Currently, approximately 90% of genital herpes is due to herpes simplex virus (HSV)-2 and the remaining 10% is caused by HSV-1. The estimated seroprevalence of HSV-2 in developed countries is approximately 15% to 25% [2,3] and that of HSV-1 is approximately 65%. The most recent studies in Spain show that the prevalence of HSV-2 (3.5%) is lower than in neighboring countries.[4]

Humans are the only reservoir for HSV infection.[2] HSV-2 is transmitted by sexual contact, both through cutaneous and mucosal lesions and through contaminated secretions with no apparent clinical manifestations, whereas HSV-1 is usually transmitted by orogenital contact. More than half of patients infected with HSV-2 experience episodes of asymptomatic viral shedding, making this mechanism the main form of transmission—reported in up to 70% of cases.[5] HSV-2 transmission from men to women is far more common than transmission from women to men.[2] Primary genital infection by both viruses is more frequent in young adults and is usually asymptomatic. Genital infection by HSV-1 is characterized by less asymptomatic viral shedding, a lower transmission rate, and a lower recurrence rate than that caused by HSV-2.[1] The fact that most transmissions are due to episodes of asymptomatic viral shedding and that the initial infections

Correspondence: José M. Martín Hernández
Servicio de Dermatología
Hospital Clínico Universitario
Avda. Blasco Ibáñez 17
46010 Valencia, Spain
jmmart@eresmas.com

Manuscript accepted for publication April 21, 2008.

also tend to be asymptomatic means that most patients who are seropositive for HSV-2 are not aware that they are infected.

Antiviral Drugs

There are currently 3 antiviral drugs approved for use in genital herpes. These are aciclovir, valaciclovir, and famciclovir.[6,7]

Oral antiviral drugs penetrate the infected cells and act as nucleoside analogs; they bind to and are phosphorylated by viral thymidine kinase. The antiviral agents are then phosphorylated again by cellular enzymes and compete with the nucleosides to bind to viral DNA polymerase, thereby inactivating the enzyme and reducing viral replication.

Aciclovir is an acyclic guanosine analog that inhibits the viral DNA polymerase enzyme by acting as a competing inhibitor of guanosine triphosphate.[8] Following oral administration, the drug is initially phosphorylated by viral thymidine kinase and, subsequently, by the cellular kinases to aciclovir triphosphate, which binds to the viral DNA polymerase, inhibiting it and acting as a DNA chain terminator.

Adverse effects of aciclovir are rare and include headache, nausea, diarrhea, and renal toxicity; patients with renal failure will therefore require adjustment of the dosage. Neuropsychiatric manifestations such as confusion, tremors, delirium, and abnormal speech have been infrequently reported.[6]

The main limitation of aciclovir is its low bioavailability (15%-20%), which means that it must be administered in frequent doses throughout the day (usually 5 doses).

Valaciclovir is a prodrug of aciclovir that has considerably greater bioavailability (65%) when taken orally and achieves levels in blood comparable to those of intravenous aciclovir.[9,10] The adverse effects are similar to those of aciclovir.

Famciclovir is a prodrug whose active metabolite is penciclovir, an acyclic guanosine analog. It undergoes a similar phosphorylation process to that of aciclovir and also inhibits viral DNA polymerase, thereby blocking viral synthesis and replication. Penciclovir triphosphate has a considerably longer intracellular half-life than aciclovir triphosphate, remaining for between 10 and 20 hours in the cells infected by the virus.[11] Famciclovir also has greater bioavailability (77%) than aciclovir or valaciclovir and has similar tolerance and adverse effects to aciclovir. In light of the natural history of HSV infection and of the high bioavailability of famciclovir and its longer half-life, early instatement of treatment with this drug can be of great help in managing recurrent HSV infection.

Allergic reactions to aciclovir, valaciclovir, and famciclovir have been reported on rare occasions.

Treatment of Initial Infection

Initial infection by genital herpes is often asymptomatic. Symptomatic primary genital herpes usually presents a week after contact with the virus, though it may present between 2 days and 3 weeks after infection. Prodromes in the form of hypoesthesias or dysesthesias (pruritus, burning sensation, pain, etc) appear between 12 and 24 hours before the appearance of the cutaneous and mucosal lesions. As there is no prior immunity, the usual initial clinical signs and symptoms consist of the appearance of papules and vesicles that rapidly evolve into numerous intensely painful erosions and ulcers with polycyclic outlines usually surrounded by an erythematous halo (Figure 1). The genital lesions are usually accompanied by painful enlarged inguinal lymph nodes and, occasionally, by systemic clinical symptoms such as fever and myalgia. Symptomatic primary herpes infection is more frequent among women and clinical signs are usually more severe than in men. The lesions usually heal spontaneously in less than 4 weeks if left untreated. The risk of infection persists until the lesions are completely healed.

The use of antiviral drugs is beneficial in most patients who present symptoms of herpes infection. These drugs achieve faster healing of the lesions and attenuate the symptoms; unfortunately, they do not eradicate the latent virus and so they cannot prevent recurrences, though they do reduce the duration and intensity.

Oral aciclovir, valaciclovir, and famciclovir can be used to treat the initial infection.

The recommended duration of treatment is between 7 and 10 days, though treatment with antiviral agents should always be continued until the ulcers have completely scarred over. The recommended dosage regimens for the treatment of primary genital infection due to HSV are shown in Table 1.[12]

The infection is usually benign and self-limiting, though complications of different types may occur in initial infections; these complications are mainly due to the hematogenous dissemination of the virus and include

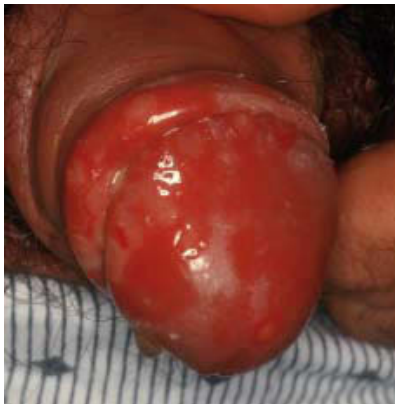

Figure 1. Initial herpes infection showing multiple erosions with polycyclic outlines, surrounded by an erythematous halo and associated with intense pain.

Table 1. Recommended Regimens for Initial Genital Herpes Infection

Aciclovir
200 mg orally, 5 times a day for 7-10 days
400 mg orally, 3 times a day for 7-10 days
Valaciclovir
1 g orally, twice a day for 7-10 days
Famciclovir
250 mg orally, 3 times a day for 7-10 days.

Adapted from the Centers for Disease Control and Prevention. *revention*[12].

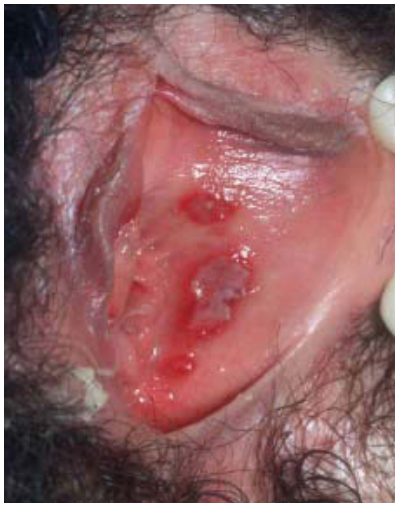

Figure 2. Erosions surrounded by an erythematous halo. Clinical signs and symptoms of recurrences are usually less intense than those of initial infection.

neurologic and psychiatric complications, generalized cutaneous involvement, and even visceral involvement (hepatitis, arthritis, pneumonitis, etc), in some cases. The most common neurologic complication is aseptic meningitis, though Guillain-Barre syndrome, encephalitis, sacrolumbar myeloradiculopathy, and transverse myelitis may also occur.

When complications occur, intravenous treatment with aciclovir is recommended, at a dosage of 5-10 mg/kg every 8 hours, usually for a period of between 7 and 10 days. If clinical symptoms improve rapidly, intravenous treatment may be substituted with oral treatment until symptoms have resolved completely.[12]

Treatment of Recurrences

Once the initial infection has occurred, the virus remains in a latent state in the sacral sensory ganglia. Recurrences of genital herpes are caused by a reactivation of this latent infection and are favored by factors such as fever, stress, or menstruation (menstrual herpes). Thus, the virus migrates from the glial cells of the dorsal ganglia, via the sensory nerve fibres, to the genital region.

Clinical recurrences occur in approximately 50% of patients carrying anti-HSV antibodies, usually from 4 months after the initial outbreak, and are much more frequent in patients with genital herpes due to HSV-2 than in those with HSV-1 infection. The risk of recurrence is greater in men, though the episodes are more painful in women.

Clinical symptoms of recurrences are less intense than those of initial infection (Figure 2) and of shorter duration, and may occasionally be different from the classic signs of vesicles and ulcers, with nonspecific clinical signs such as irritation, edema, scabs, or fissures.[13]

While no definitive cure for HSV infection exists to date, there are essentially 2 therapeutic strategies for managing recurrences of genital herpes; these involve either treating the outbreaks when they occur (episodic therapy) or trying to prevent future outbreaks (suppressive therapy).

Episodic therapy is carried out when the symptoms of an outbreak occur. When treating recurrences, an antiviral drug is administered orally for several days (usually between 3 and 5 days) with the aim of reducing the duration of the episode and alleviating the symptoms of the infection, though the frequency of the recurrences is not affected. Where possible, treatment should be instated as soon as prodromes appear or on the same day the lesions appear. This therapy has no effect on subclinical episodes and has not been shown to reduce the risk of transmission. Episodic therapy is appropriate for people with infrequent or mild recurrences who do not require daily medication, are not concerned by the frequency of the recurrences, or are not sexually active.[14]

However, if the aim is to reduce the number of recurrences or reduce the risk of transmission of genital herpes to sexual partners, suppressive therapy is recommended.[15-17] This therapeutic strategy consists of administering an antiviral drug daily in order to prevent reactivation of the virus. This strategy is recommended in patients with more than 6 episodes a year; in these patients, the frequency of episodes can be reduced by between 70% and 80%.[18,19]

Suppressive therapy can also be used intermittently by administering the drug for a limited period of time to reduce the probability of an outbreak in a specific period of the patient's life, such as when giving birth.

Suppressive therapy is appropriate for patients with multiple or severe recurrences, for patients who become anxious about the possibility of recurrences, or patients who are worried about the possibility of transmitting the infection to sexual partners. The recommended dosage regimens are shown in Table 2.[12]

The decision to use either episodic or suppressive therapy to manage recurrences of genital herpes requires agreement between patient and physician.

It should be remembered that virus replication is most active in the first 24 hours after the lesions appear, when most of the lesions are at the vesicle stage. Therefore, the best time to obtain clinical benefit from antiviral agents is in the short period of time in which viral replication predominates over the host's immune response, which also develops rapidly. For this reason, antiviral therapy should be instated very early on in order to obtain maximum benefit; the best strategy consists of educating patients to have the medication available and to self-administer it as soon as possible after they notice the prodromal symptoms.[14,20,21]

Of the different treatment options used as episodic therapy, aciclovir has been approved for use for 5 days, though it has also been shown to be effective when administered for only 2 days.[17] Aciclovir is effective but its low bioavailability requires very frequent doses. Valaciclovir has greater bioavailability than aciclovir and has been approved for episodic therapy in a 3-day regimen. The high bioavailability of famciclovir (77%), together with the rapid onset of viral replication, makes this drug very effective in the treatment of outbreaks of genital herpes. Moreover, its pharmacokinetics allow for ease of administration and the treatment is much simpler to follow than with other antiviral drugs.[11,20,22]

Several recent clinical trials have shown that high-dose regimens of antiviral therapy with famciclovir, administered for just 1 day, are also effective for both episodic treatment of outbreaks of genital herpes (famciclovir, 1 g twice a day) and herpes labialis (famciclovir, 1.5 g once a day).[21]

The regimen of famciclovir for a single day appears to inhibit viral replication sufficiently to significantly reduce both the symptoms and the tissue damage that are characteristic of a full outbreak, thereby preventing progression to a full recurrence in some cases. This form of administration has the great advantage that the drug need only be administered on 1 day, unlike conventional regimens of episodic therapy, which last from 3 to 5 days. The level of compliance with the treatment and patient satisfaction improve, and improved overall management of recurrences of genital herpes may be possible.

Although there are no studies that compare famciclovir 1-day treatment with other antiviral agents, patients who received this treatment experienced similar effects to those observed with traditional, longer therapies.[14,23-29]

Finally, when comparing suppressive therapy with valaciclovir and episodic therapy with valaciclovir, suppressive therapy showed a greater impact on outcomes such as frequency of recurrence and burning sensation. Both types of therapy considerably improved the quality of life of patients with recurrent genital herpes; both strategies are therefore beneficial in patients with recurrent herpes.[30]

Furthermore, valaciclovir appears to be slightly better than famciclovir in suppressive treatment of genital herpes and in reducing viral shedding.[17] The recommended regimens for episodic treatment of genital herpes are shown in Table 3.[12]

Table 2. Recommended Regimens for Suppressive Treatment of Genital Herpes

Aciclovir
400 mg orally, twice a day
Valaciclovir
500 mg orally, once a day
1 g orally, once a day
Famciclovir
250 mg orally, twice a day

Adapted from the Centers for Disease Control and Prevention[12].

Genital Herpes and Pregnancy

Approximately 2% of women infected with HSV-2 come into contact with the virus during pregnancy.[31] Ninety percent of these women are underdiagnosed because they are asymptomatic or have subtle symptoms that are confused with those of other diseases. Correct diagnosis in these cases requires laboratory techniques such as cultures, polymerase chain reaction (PCR), and specific serology.[32,33]

The risk of transmission by the mother to the neonate is very high (30%-50%) if the mother acquires herpes close to the time of birth. The risk is much lower (<1%), however, in women with a history of recurrent herpes or who became infected during the first trimester of the pregnancy.[12,34] Nevertheless, because it is much more frequent for the mother to suffer from a recurrence of herpes rather than an initial infection during pregnancy, the proportion of infection due to genital herpes in neonates is much higher as a result of a recurrence of herpes in the mother.

Transmission of HSV to the neonate may occur both in cases of maternal asymptomatic episodes and in cases of asymptomatic viral shedding.[35,36] In women who are seropositive for HSV-2, the prevalence of asymptomatic shedding during delivery, measured by means of HSV cultures, varies between 0.35% and 1.4%,[37] though it may reach 10% when measured using PCR (to detect HSV

Table 3. Recommended Regimens for Episodic Treatment of Genital Herpes

Aciclovir
400 mg orally, 3 times a day for 5 days
800 mg orally, twice a day for 5 days
800 mg orally, 3 times a day for 2 days
Valaciclovir
500 mg orally, twice a day for 3 days
1 g orally, once a day for 5 days
Famciclovir
125 mg orally, twice a day for 5 days
1 g orally, twice a day for 1 day

Adapted from the Centers for Disease Control and Prevention.[12]

DNA).[38] The probability of acquiring genital herpes during pregnancy is identical in all 3 trimesters.[36]

The safety of aciclovir, valaciclovir, and famciclovir in pregnant women has not been fully established to date. The available data on women who have received aciclovir in the first trimester of pregnancy suggest that there is no increase in the risk of fetal malformation compared to the general population; the drug therefore offers certain guarantees in pregnancy. Experience with valaciclovir and famciclovir is much more limited.[12,39]

Antiviral therapy is used in pregnant women essentially in 2 circumstances: to treat severe or disseminated disease or a primary infection and to prevent a recurrence at the end of the pregnancy and thereby prevent neonatal herpes. Aciclovir may be administered orally to pregnant women suffering from an initial episode of genital herpes or from a moderate to severe recurrence, or intravenously in very severe cases. Moreover, treatment with aciclovir at the end of pregnancy reduces the frequency of cesarean delivery in women with recurrent genital herpes by reducing the probability of a recurrence at the time of delivery.[34] In initial infection or a first recurrent genital episode, the recommended regimen is 400 mg of oral aciclovir 3 times a day for 10 days, or 5 mg/kg of intravenous aciclovir 3 times a day for 10 days in very severe cases. In these cases, suppressive treatment at the end of pregnancy is also recommended with 400 mg of aciclovir 3 times a day from week 36 to the time of delivery.[12,38,40,41]

Although suppressive therapy during pregnancy has traditionally been carried out using aciclovir, as it is the most thoroughly studied of all the antiviral agents, several studies have appeared in recent years using 500 mg of oral valaciclovir twice a day from week 36 of pregnancy, showing that this drug also significantly reduces shedding of HSV and recurrences that require cesarean delivery.[42,43]

Although there is some disagreement regarding the need to treat mild recurrences at the beginning of pregnancy, most authors agree that recurrences should be treated. The most commonly used regimen is 200 mg of aciclovir 5 times a day for 5 days, except in severe cases, in which treatment should be intravenous. Suppressive therapy in women diagnosed with genital herpes is indicated from week 36 in order to prevent a recurrence at the time of delivery. Although infection is also possible in the event of asymptomatic shedding at the time of delivery, there is no evidence to support the use of antiviral agents in women who are seropositive for HSV but have no history of genital herpes.[12]

Cesarean delivery is currently reserved for cases where there are lesions in the genital area of the mother at the time of delivery or, where genital herpetic lesions are absent, if initial infection or a first genital episode has occurred in the month prior to delivery. Nevertheless, cesarean delivery does not completely eliminate the risk of transmitting herpes to the neonate. In some studies, between 13% and 33% of neonates with HSV infection were delivered by cesarean section.[34,44] If the mother has herpetic lesions or a history of genital herpes, pharyngeal and ocular cultures and a detailed clinical examination of the neonate should be performed. Intravenous treatment of the neonate should be instated early in all cases of neonatal herpes or where there are clear risk factors. The recommended regimen is 20 mg/kg of intravenous aciclovir every 8 hours for 21 days in cases of disseminated disease or involvement of the central nervous system, or for 14 days where the disease is limited to the skin and mucosa.[12,45]

Weekly cultures are not recommended in pregnant women with confirmed genital herpes as these cultures do not predict the risk of acquisition of HSV by the neonate because asymptomatic shedding at the time of delivery is not prevented. Nevertheless, suppression with antiviral agents during pregnancy reduces the possibility of both clinical lesions at the time of delivery and subclinical shedding, and therefore also reduces the number of cesarean deliveries.[32,46,47] Invasive fetal monitoring may increase the risk of neonatal herpes and should only be used in HSV-2 seropositive women with very well-defined obstetric indications.[48]

Prevention of mother-fetus transmission of HSV should be based on preventing maternal infection at the end of pregnancy and in preventing the neonate from coming into contact with the herpetic lesions at the moment of birth.[49]

Performing serology makes it possible to detect women at risk. An HSV-seropositive woman risks acquiring the infection if her partner is seropositive for HSV-2 or HSV-1.[5]

Several studies have shown that, in HSV-2 seropositive women with HSV-2 seropositive partners, the risk of acquiring an infection due to HSV-2 during pregnancy is between 20% and 30%.[34,50] As in the rest of the nonpregnant

population infected with HSV, most seroconversions are asymptomatic or go unnoticed.[36] However, this risk is considerably reduced (to between 5% and 10%) if the woman is HSV-1 seropositive, even though her partner is HSV-2 seropositive.[5,36]

Women who are susceptible to acquiring genital herpes should avoid unprotected coitus or practice sexual abstinence during the third trimester. HSV-2 seropositive pregnant women should be examined as a precaution at the end of the pregnancy to search for genital lesions and should be questioned about prodromes at the time of delivery. If evidence of genital lesions or prodromes is found, cesarean section should be performed.[12,51,52]

Finally, in discordant couples (seronegative woman and HSV-2 seropositive man), suppressive therapy with 500 mg of valaciclovir a day has been shown to be effective in reducing transmission of HSV during pregnancy.[15]

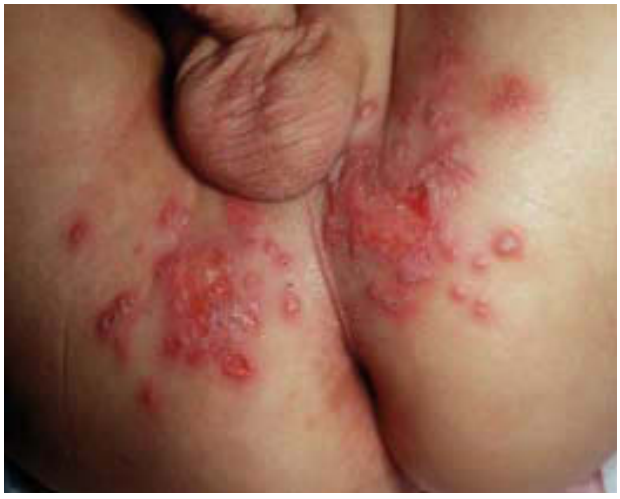

Figure 3. Initial genital herpes infection in children. Sexual abuse must be ruled out in these cases.

Genital Herpes in Children

Genital herpes is a rare disease in children and is mainly associated with infection by HSV-1. Asymptomatic carriers are also frequently implicated in the transmission of the virus. In infancy, genital transmission of HSV generally occurs through autoinoculation or via persons infected with HSV-1[53-55] (Figure 3). It is important that parents with a history of HSV-1 infection, particularly when located on the lips or hands, understand that they can infect their children with genital herpes if they kiss or touch them with active lesions, and that they can also transmit the disease in cases of asymptomatic viral shedding.

As in adults, the infection is usually asymptomatic. Genital herpes most commonly presents in children between the ages of 2 and 4 years. As most cases involve infection with HSV-1, recurrences are rare.

In children and adolescents, it is particularly important to perform serology and cultures to determine which type of HSV has caused the infection. The possibility of sexual abuse should, of course, be considered and, in these cases, the child should be evaluated by a forensic physician. Sexual abuse is most frequent in children aged between 6 and 12 years.[53-55]

The same drugs can be used to treat genital herpes in children as in adults. The dosages used in children over 2 years are similar to those used in adults, whereas in children under 2 years, the dosage should be halved: 2.5 mL of aciclovir in suspension, equivalent to 200 mg.

Genital Herpes in Immunocompromised Patients

Patients with neutropenia or T-cell dysfunction or deficiency are more susceptible to herpes simplex infection. In immunocompetent patients, the process lasts between approximately 7 and 10 days, whereas in cases of abnormal immunity, the clinical picture may vary considerably; thus, the frequency and severity of HSV infections are proportional to the level of immunosuppression, and are proportional to the CD4 cell count in patients infected with HIV.[56]

A large proportion of patients infected with type-1 HIV (HIV-1) are also infected with HSV-2, ranging between 50% and 90% in different parts of the world.[1,57,58] In fact genital herpes is the most frequent sexually transmitted disease among HIV-positive patients.[59] The presence of inflammation and ulceration of the mucosa facilitates transmission of HIV to sexual partners and, furthermore, acute HSV infection or reactivation of a previous infection stimulates HIV replication, thus increasing the viral load in plasma and favoring progression of the disease.[60]

Genital herpes in patients with HIV infection is associated with a more severe infection and lesions that are more chronic, and with increased asymptomatic shedding. Genital ulcers in immunocompromised patients may be numerous, reach a very large size, and be associated with intense pain and a considerable degree of lymph node involvement (Figure 4). Atypical forms of presentation, such as hyperkeratotic lesions, lesions similar to condylomata acuminata, or even epidermoid carcinoma are also common. HIV-induced immunosuppression, particularly when the CD4 count is below 100 cells/mm^3, plays an important role in the reactivation of genital herpes and is also responsible for these rare forms of presentation and the more chronic course of the lesions.[61,62] An increase has also been reported in the incidence of genital herpes following the introduction of antiretroviral therapy for HIV. This circumstance would represent a frequent

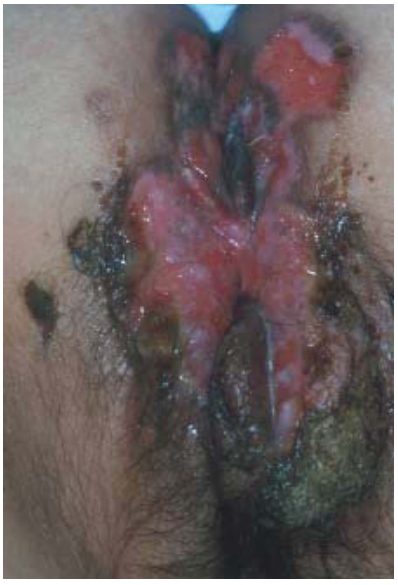

Figure 4. Genital herpes in a patient with HIV infection. Genital ulcers in immunocompromised patients are usually numerous and may reach a very large size and be associated with intense pain.

manifestation of immune reconstitution inflammatory syndrome in patients infected with HIV.[63]

Recurrences of genital ulcers in HIV-positive patients are between 3 and 5 times more frequent than in immunocompetent patients.[64] Nucleoside analogs reduce the frequency and severity of HSV-2 recurrences and also reduce levels of HIV-1 in the blood and genital tract. These drugs are safe and well tolerated in patients with HIV-1 infection. Due to these benefits, serology for HSV-2 should be performed on all patients with HIV infection.[57] The main therapeutic difference in immunocompromised patients is that the drugs must be administered for a longer period of time in order to cure lesions. In complicated infections or cases of hematogenous dissemination, treatment should be administered intravenously and in a hospital setting, with aciclovir at a dosage of 10 mg/kg every 8 hours for 10 days.

Resistance to these antiviral drugs frequently develops in immunocompromised patients, particularly if they have been repeatedly treated with them. Resistance has been detected in between approximately 5% and 25%[6] of patients with HIV infection and genital herpes, and is more frequent in patients who receive episodic treatment.[65] In most cases, resistance is due to the selection of defective strains of viral thymidine kinase—the enzyme required to activate aciclovir by phosphorylation. However, these strains are usually sensitive to foscarnet and cidofovir, as these drugs act on the DNA polymerase of the virus.[65]

Thus, in cases of herpetic lesions that do not heal, it is important to isolate the virus in order to determine its sensitivity and instate appropriate treatment. In general, resistance to aciclovir is also accompanied by resistance to valaciclovir and famciclovir. In these cases, the alternative is foscarnet administered intravenously at a dosage of 40 mg/kg every 8 hours until symptoms resolve. It should be remembered that foscarnet is nephrotoxic and that resistance to the drug has been reported in HIV-positive patients.

Cidofovir is another antiviral drug that is being used both intravenously and topically in herpes infections that do not respond to conventional antiviral agents.[66]

In cases of local infection, the usual regimens may be applied for 10 days. If clinical signs and symptoms have not remitted after 10 days, treatment with intravenous aciclovir may be instated; if the latter treatment is also shown not to be effective, resistance to aciclovir should be considered and an alternative drug, such as foscarnet, should be used.

Because lesions in immunocompromised patients are more extensive and deeper, superinfection by bacteria and fungi is common and these lesions should therefore be treated with appropriate antibiotic therapy or antifungal agents.

The recommended regimens for treating recurrences in HIV-positive patients are shown in Table 4.[12]

In organ transplant patients, infection due to HSV-1 and HSV-2 is the only infection that characteristically shows increased incidence in the first weeks after surgery.[67] For this reason, patients scheduled for organ transplant surgery should receive preoperative prophylactic treatment with aciclovir, thereby significantly reducing infection or reactivation not only of HSV-1 and HSV-2 but also of other herpesviruses, such as cytomegalovirus.[68,69] Prophylaxis with intravenous aciclovir or oral valaciclovir (500 mg/12 h) is recommended in seropositive patients scheduled for transplant surgery.

Herpes proctitis is treated with high doses of aciclovir and the recommended regimen is 400 mg orally, 5 times a day for between 7 and 10 days.

Advice on Reducing Transmission

Educating patients with genital herpes regarding some important aspects of the disease can reduce the risk of transmission. This advice should be based on encouraging patients to inform both previous and successive partners of their situation, practice sexual abstinence during outbreaks, and use barrier methods, and on providing the option of suppressive therapy.

Patients and their partners should understand that sexual transmission of HSV can occur during asymptomatic periods and that asymptomatic viral shedding is much more frequent in the 12 months after infection. Serology should be recommended to asymptomatic partners of infected patients in order to determine whether they are at risk of infection. Evidently, sexual relations should be avoided when symptoms of the infection, including prodromes, are present. Latex condoms, when used

consistently and correctly, can reduce the risk of transmission of genital herpes, though they do not provide 100% protection; they should also be used between outbreaks.

Furthermore, the risk of neonatal infection should be explained to all patients, including men. Pregnant women who are not infected by HSV-2 should avoid sexual relations during the third trimester with partners with a history of genital herpes. Similarly, pregnant women who are not infected by HSV-1 should also avoid exposure of their genitals to HSV-1, essentially by not receiving oral sex during the third trimester from a partner with herpes labialis.[36]

Finally, patients should know that the risk of sexual transmission of HSV-2 may be reduced by daily use of antiviral agents by the infected person.[15]

Table 4. Recommended Regimens for Treatment of Recurrences in HIV-Positive Patients

Suppressive Treatment	
Aciclovir:	400-800 mg orally, 2 or 3 times a day
Valaciclovir:	500 mg orally, twice a day
Famciclovir:	500 mg orally, twice a day
Episodic Treatment	
Aciclovir:	400 mg orally, 3 times a day for 5-10 days
Valaciclovir:	1 g orally, twice a day for 5-10 days
Famciclovir:	500 mg orally, twice a day for 5-10 days

Adapted from the Centers for Disease Control and Prevention.[12] .

Topical Treatment of Genital Herpes

Topical treatments play only a limited role among the range of therapeutic options available for treating genital herpes. Although topical treatment with aciclovir was initially used in recurrent genital herpes, it has been shown to be ineffective; therefore, while it is approved for the treatment of genital herpes, its use is not recommended.[70]

The use of poultices may lead to improvement of exudative lesions and topical antibiotics or antifungal agents are of considerable benefit in preventing and treating superinfections, especially in cases of extensive or deep lesions.

Different topical treatments have been used in patients (especially immunocompromised patients) with recurrent herpes and resistance to aciclovir. Cases have been reported of genital herpes refractory to aciclovir in patients with AIDS, who have been successfully treated with imiquimod,[71-73] though this drug does not appear to alter the natural history of genital herpes according to some clinical studies.[74]

Cases have also been reported of resistance to aciclovir and oral valaciclovir in patients with AIDS and severe genital herpes, in whom the lesions resolved within 2 months of twice daily application of 2.4% foscarnet cream for 20 minutes. In some trials, 1% foscarnet cream 5 times a day was also used, with a good response but with some adverse effects such as irritation, headache, and fever.[75]

Cases have also been reported of HIV-positive patients with genital herpes resistant to aciclovir and valaciclovir, in whom hypertrophic lesions similar to condylomata disappeared in less than 2 months after using 1% cidofovir cream twice a day and 50% foscarnet solution, also applied twice a day for 1 month.[71] Foscarnet in solution appears to be a well tolerated treatment with fewer adverse effects than the cream formulation. These drugs have the disadvantage of a very short half-life, though the number of applications can be increased if necessary.[71,72]

The literature contains several reports in which resistance of HSV-2 to aciclovir and to valaciclovir disappeared after using this type of topical treatment, especially foscarnet; topical treatments would therefore be of considerable benefit in the management of immunocompromised patients with resistance to antiviral drugs.[76-78]

Anecdotal evidence suggests that povidone iodine has also been beneficial in the treatment of some cases of genital herpes.[79]

Studies using interference RNA to prevent infection of the vaginal mucosa of mice have been performed in recent years. This has led to the possibility of research to develop microbicides with interference RNA that will be able to block the virus when it enters the body.[80,81]

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Severson JL, Tyring SK. Relation between herpes simplex viruses and human immunodeficiency virus infections. Arch Dermatol. 1999;135:1393-7.
2. Milpied B, Javier M, Derancourt CH, Verret JL, Caumes E, Bouscarat F. Herpes genital. Ann Dermatol Venereol. 2006; 133:S28-30.
3. Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, et al. Herpes simplex virus type 2 in the United States, 1976-1994. N Engl J Med. 1997;337: 1105-11.
4. Velasco M. Actualización del herpes genital. Epidemiología del herpes genital. XIII Reunión del Grupo Español para la Investigación de las Enfermedades de Transmisión Sexual. Valencia; 2007.

5. Mertz GJ, Benedetti J, Ashley R, Selke SA, Corey L. Risk factors for the sexual transmission of genital herpes. Ann Intern Med. 1992;116:197-202.
6. Ferrán M, Pujol RM. Tratamiento del herpes zóster. Actas Dermosifiliogr. 2006;97 Supl 3:25-37.
7. España A, Redondo P. Actualización en el tratamiento del herpes zóster. Actas Dermosifiliogr. 2006;97:103-14.
8. McKendrick MW, McGill JI, White JE, Wood MJ. Oral acyclovir in acute herpes zoster. Br Med J. 1986;293: 1529-32.
9. Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrobiol Agents Chemother. 1995;39:1546-53.
10. Perry CM, Faulds D. Valaciclovir: A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in herpesvirus infections. Drugs. 1996;52:754-72.
11. Earnshaw DL, Bacon TH, Darlison SJ, Edmonds K, Perkins RM, Vere Hodge RA. Mode of antiviral action of penciclovir in MRC-5 cells infected with herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus. Antimicrob Agents Chemother. 1992;36:2747-57.
12. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. MMWR. 2006; 55:16-20.
13. Ashley RL, Wald A. Herpes genital: review of the epidemic and potential use of type-specific serology. Clin Microbiol Rev. 1999;12:1-8.
14. Tyring S, Richwald G, Hamed K. Single-day therapy: an expert opinion on a recent development for the episodic treatment of recurrent genital herpes. Arch Gynecol Obstet. 2007;275:1-3.
15. Corey L, Wald A, Patel R, Sacks SL, Tyring SK, Warren T, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11-20.
16. Fife KH, Warren TJ, Ferrera RD, Young DC, Justus SE, Heitman CK, et al. Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc. 2006;81: 1321-7.
17. Wald A, Selke S, Warren T, Aoki FY, Sacks S, Díaz-Mitoma F, et al. Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and virus shedding. Sex Transm Dis. 2006;33:529-33.
18. Díaz-Mitoma F, Sibbald G, Shafran SD, Boon R, Saltzman RL. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. JAMA. 1998;280: 887-92.
19. Reitano M, Tyring S, Lang W, Thoming C, Worm AM, Borelli S, et al. Valacyclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. J Infect Dis. 1998;178:603-10.
20. Sacks SL, Aoki FY, Díaz-Mitoma F, Sellors J, Shafran SD. Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes. JAMA. 1996;276:44-9.
21. Whitley RJ. New approaches to the therapy of HVS infections. Herpes. 2006;13:2.
22. Pue MA, Benet MA. Pharmacokinetics of famciclovir in man. Antivir Chem Chemother. 1993;4 Suppl 1:47-55.
23. Spruance SI, Bodsworth N, Resnick H, Conant M, Oeuvray C, Gao J, et al. Single-dose, patient-initiated famciclovir: a randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. J Am Acad Dermatol. 2006;55:47-53.
24. Spruance S, Aoki FY, Tyring S, Stanberry L, Whitley R, Hamed K. Short-course therapy for recurrent genital herpes and herpes labialis. J Fam Pract. 2007;56:30-6.
25. Aoki FY, Tyring S, Díaz-Mitoma F, Gross G, Gao J, Hamed K. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2006;42:8-13.
26. Whitley R, Díaz-Mitoma F, Hamed K. Single-day famciclovir therapy for recurrent genital herpes. Curr Med Res Opin. 2006;22:1307-10.
27. Vinh DC, Aoki FY. Famciclovir for the treatment of recurrent genital herpes: a clinical and pharmacological perspective. Expert Opin Pharmacother. 2006;7:2271-86.
28. Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. Drugs. 2006;6:2397-416.
29. Reichman RC, Badger GJ, Mertz GJ. Treatment of recurrent genital herpes simplex infections with oral acyclovir. A controlled trial. JAMA. 1984;251:2103-7.
30. Fife KH, Almekinder J, Ofner S. A comparison of one year of episodic or suppressive treatment of recurrent genital herpes with valacyclovir. Sex Trasm Dis. 2007;34:297-301.
31. Brown ZA, Gardella C, Wald A, Morrow RA, Corey L. Genital herpes complicating pregnancy. Obstet Gynecol. 2005;106:845-56.
32. Del Boz J, Affumicato L, Martín T, Moreno-Pérez D, Vera A. Herpes simple zosteriforme neonatal. Actas Dermosifiliogr. 2008;99:157-69.
33. Requena L. Diagnóstico y diagnóstico diferencial del herpes zóster. Actas Dermosifiliogr. 2006;97 Supl 3:17-24.
34. Brown Z. Preventing herpes simplex virus transmission to the neonate. Herpes. 2004;11 Suppl 3:175A-86A.
35. Brown ZA, Benedetti J, Ashley R, Burchett S, Selke S, Berry S, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. N Engl J Med. 1991;324:1247-52.
36. Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med. 1997;337:509-15.
37. Brown ZA. HVS-2 specific serology should be offered routinely to antenatal patients. Rev Med Virol. 2000;10:141-4.
38. Watts DH, Brown Z, Money D, Selke S, Huang ML, Sacks SL, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and caesarean delivery. Am J Obstet Gynecol. 2003;188:836-43.
39. Stone KM, Reiff-Eldridge R, White AD, Cordero JF, Brown Z, Alexander ER, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984-1989. Birth Defects Research (Part A). 2004;70:201-7.
40. Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD Jr. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstet Gynecol. 2003;102:1396-403.
41. Scott LL, Hollier LM, McIntire D, Sánchez PJ, Jackson GL, Wendel GD Jr. Acyclovir suppression to prevent genital recurrent herpes at delivery. Infect Dis Obstet Gynecol. 2002;10: 71-7.

42. Sheffield JS, Hill JB, Hollier LM. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. Obstet Gynecol. 2006;108:141-7.
43. Andrews WW, Kimberlin DF, Whitley R, Cliver S, Ramsey PS, Deeter R. Valacyclovir therapy to reduce recurrent genital herpes in pregnant women. Am J Obstet Gynecol. 2006; 194:774-81.
44. Fonnest G, de la Fuente, Fonnest I, Weber T. Neonatal herpes in Denmark 1977-1991. Acta Obstet Gynecol Scand. 1997;76:335-58.
45. Kesson AM. Management of neonatal herpes simplex virus infection. Paediatr Drugs. 2001;3:81-90.
46. Scott LL, Sánchez PJ, Jackson GL, Zeray F, Wendel GD. Acyclovir suppression to prevent caesarean delivery after first-episode genital herpes. Obstet Gynecol. 1996;87: 69-73.
47. Braig S, Luton D, Sibony O, Edlinger C, Boissinot C, Blot P, et al. Acyclovir prophylaxis in late pregnancy prevents recurrent genital herpes and viral shedding. Eur J Obstet Gynecol Reprod Biol. 2001;96:55-8.
48. Parvey LS, Chien LT. Neonatal herpes simplex virus infection introduced by fetal-monitor scalp electrodes. Pediatrics. 1980;65:150-3.
49. Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 1: Herpes simplex virus infections. Med Microbiol Immunol. 2007;196:95-102.
50. Prober CG, Sullender WM, Yasukawa LL, Au DS, Yeager AS, Arvin AM. Low risk of herpes simplex virus infections in neonates exposed to the virus at the time of vaginal delivery to mothers with recurrent genital herpes simplex virus infections. N Engl J Med. 1987:316:240-4.
51. Libman MD, Dascal A, Kramer MS, Mendelson J. Strategies for the prevention of neonatal infection with herpes simplex virus: a decision analysis. Rev Infect Dis. 1991;13: 1093-104.
52. Hutto C, Arvin A, Jacobs R, Steele R, Stagno S, Lyrene R, et al. Intrauterine herpes simplex virus infections. J Pediatr. 1987;110:97-101.
53. Khaddar RK, Bradri T, Ben Hassen A, Bouraouri S, Souissi A, Ben Tekaya N, et al. Genital primary herpetic infection in an infant: clinical features, diagnosis and management. Dermatol Online J. 2005;11:22.
54. Taieb A, Body S, Astar I, DuPasquier P, Maleville J. Clinical epidemiology of symptomatic primary herpetic infection in children. A study of 50 cases. Acta Paediatr Scand. 1987;76: 128-32.
55. Anderson C. Childhood sexually transmited diseases: one consequence of sexual abuse. Public Health Nurs. 1995;12: 41-6.
56. Bagdades EK, Pillay D, Squire SB, O'Neil C, Johnson MA, Griffiths PD. Relationship between herpes simplex virus ulceration and CD4 cell counts in patients with HIV infection. AIDS. 1992;6:1317-20.
57. Strick LB, Wald A, Celum C. Management of herpes simplex virus type 2 infection in VIH type 1-infected presons. Clin Infect Dis. 2006;43:347-56.
58. Mertz GJ. Epidemiology of genital herpes infections. Infect Dis Clin North Am. 1993;7:825-39.
59. O'Farrell N, Tovey SJ. High accumulative incidence of genital herpes amongst HIV-1 seropositive heterosexuals in south London. Int J STD AIDS. 1994;5:415-8.
60. Heng MC, Heng SY, Allen SG. Co-infection and synergy of human immunodeficiency virus-1 and herpes simplex virus-1. Lancet. 1994;343:255-8.
61. Vogel P, Smith KJ, Skeleton HG, Cuozzo D, Wagner KF. Verucous lesions of herpes simplex in HIV-1 patients. Int J Dermatol. 1993;32:680-2.
62. Monteagudo B, López-Mouriño VM, Ordóñez P, Durana C, de las Heras C, Cacharrón JM. Úlceras herpéticas perianales en un paciente con infección por el virus de inmunodeficiencia humana no diagnosticado previamente. Actas Dermosifiliogr. 2006;97:479-80.
63. Couppie P, Sarazin F, Clyti E, El Guedj M, Vaz T, Clyti E, et al. Increased incidence of genital herpes after HAART initiation: a frequent presentation of immune reconstitution inflammatory syndrome (IRIS) in VIH-infected patients. AIDS Patient Care STDS. 2006;20:143-5.
64. Augenbraun M, Feldman J, Chirgwin K, Zenilman J, Clarke L, De Hovitz J, et al. Increased genital shedding of herpes-simplex virus type 2 in HIV-women. Ann Intern Med. 1995; 123:845-7.
65. File KH, Crumpacker CS, Mertz GJ, Hill EL, Boone GS. Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years suppression with acyclovir. Acyclovir Study Group. J Infect Dis. 1994;169: 1338-41.
66. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002; MMWR. 2002; 51:1-84.
67. Snydman DR. Infection in solid organ transplantation. Transpl Infect Dis. 1999;1:21-8.
68. Dykewicz CA. Preventing opportunistic infections in bone marrow transplant recipients. Transpl Infect Dis. 1999;1:40-9.
69. Celkan T, Ozkan A, Apak H, Ildiz I. Antiviral prophylaxis with continuous low dose acyclovir in childhood cancer. Leuk Lymphoma. 2006;47:1418-20.
70. Reichman RC, Badger GJ, Guinan ME. Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. J Infect Dis. 1983;147:336-40.
71. Abbo L, Vicek V, Dickinson G, Shresthe N, Doblecki S, Haslett PA. Selective defect in plasmacyoid dendritic cell function in a patient with AIDS-associated atypical genital herpes simplex vegetans treated with imiquimod. Clin Infect Dis. 2007;44:e25-7.
72. Brummitt CF. Imiquimod 5 % cream for the treatment of recurrent, acyclovir-resistant genital herpes. Clin Infect Dis. 2006;42:575.
73. Gilbert J, Drehs MM, Weinberg JM. Topical imiquimod for acyclovir-unresponsive herpes simplex virus 2 infection. Arch Dermatol. 2001;137:1015-7.
74. Schacker TW, Conant M, Thoming C, Stanczak T, Wang Z, Smith M. Imiquimod 5-percent cream does not alter the natural history of recurrent herpes genitalis: a phase II, randomized, double-blind, placebo-controlled study. Antimicrob Agents Chemother. 2002;46:3243-8.
75. Javaly K, Wohlfeiler M, Kalayjian R. Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. J Acquir Immune Defic Syndr. 1999;21: 301-6.
76. Ghislanzoni M, Cusini M, Zerboni R, Alessi E. Chronic hypertrophic acyclovir-resistant genital herpes treated with

topical cidofovir and with topical foscarnet at recurrence in an VIH-positive man. J Eur Acad Dermatol Venereol. 2006;20: 887-9.
77. Pechere M, Wunderly W, Trellu-Toutous L, Harms M, Saura JH, Krischer J. Treatment of acyclovir-resistant herpetic ulceration with topical foscarnet and antiviral sensitivity analysis. Dermatology. 1998;197:278-80.
78. Bevilacqua F, Marcello A, Toni M, Zavattoni M, Cusini M, Zerboni R, et al. Acyclovir resistance/susceptibility in herpessimplex virus type 2 sequential isolates from an AIDS patient. J Acquir Immune Defic Syndr. 1991;4:967-9.
79. Waters LJ, Barton SE, Boag FC. Betadine for herpes simplex infection. Int J STD AIDS. 2006;17:854-5.
80. Palliser D, Chowdhury D, Wang QY. An si-RNA-based microbicide protects mice from lethal herpes simplex virus 2 infection. Nature. 2006;439:89-94.
81. Johnson DC. Silencing herpes simplex virus with a vaginal microbicide. N Engl J Med. 2006;354:970-1.