S Afr Gen Pract. 2024;5(1):25-32
https://doi.org/10.36303/SAGP.0463

S Afr Gen Pract
ISSN 2706-9613 EISSN 2706-9621

REVIEW

Treatment and prevention of herpes simplex virus type 1 in immunocompetent adolescents and adults

A Wald,[1] C Johnston[2]

[1] *Professor of Medicine, Epidemiology, and Laboratory Medicine, University of Washington, United States of America*
[2] *Associate Professor of Medicine, University of Washington, United States of America*

Introduction

Herpes simplex virus type 1 (HSV-1) is a cause of recurrent vesiculoulcerative lesions of the oral or genital mucosa. It can also cause infection in the eye, skin, central nervous system, and/or visceral organs.

This topic will review treatment and prevention of primary and recurrent HSV-1 infections in immunocompetent adolescents and adults. The epidemiology and clinical manifestations of HSV-1, as well as the treatment of HSV-1 infections in young children, are discussed elsewhere. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection" and "Herpetic gingivostomatitis in young children".)

Treatment of HSV-1 infection

General principles — The management of HSV-1 infection in the immunocompetent host depends upon a variety of considerations, including:

- Whether the patient has primary HSV-1 infection or reactivation disease
- The severity of symptoms
- The site of infection (eg, mucosal versus disseminated disease)
- The frequency of recurrences

Antiviral agents for HSV infection include acyclovir, valacyclovir, and famciclovir. Metabolites of these nucleoside derivatives interfere with the synthesis of viral DNA by inhibiting viral DNA polymerase.[1] Of all the human herpesviruses, acyclovir has the greatest in vitro activity against HSV-1 and HSV-2. However, famciclovir and valacyclovir have greater oral bioavailability than acyclovir[1] and are dosed less frequently.

Oral agents are generally very well tolerated; however, gastrointestinal side effects or headache may occur. The margin of safety and tolerability of these oral antiviral medications is excellent, since these medications are selectively converted to active compounds only within the virally infected cells.

With all of these agents, dose adjustment is needed in moderate to severe renal insufficiency, since acyclovir and its analogues are dependent upon renal function for clearance. Dose adjustments are described in the Lexicomp drug information topics within UpToDate. Additional discussions on the use of acyclovir and its analogues are presented elsewhere. (See "Acyclovir: An overview" and "Valacyclovir: An overview" and "Famciclovir: An overview".)

Oral infection

Primary infection — The classic clinical manifestation of primary oral HSV-1 infection (ie, initial HSV infection in a seronegative host) is gingivostomatitis, which may be associated with pharyngitis. Although gingivostomatitis and pharyngitis are self-limited illnesses, severe infection can lead to significant oral pain and dehydration. Symptomatic primary HSV infections are associated with an increased risk of constitutional symptoms, a longer duration of lesions, and prolonged viral shedding compared with recurrent disease. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Primary infection'.)

Whom to treat — We recommend antiviral therapy for patients with evidence of primary gingivostomatitis who present within 72 hours of symptom onset. Early antiviral therapy leads to faster healing of lesions, decreased pain, and a shorter duration of fever. However, antiviral therapy should still be offered if a patient presents with new lesions and/or significant pain after this time frame.

Most of the available data on the efficacy of antiviral treatment of primary oral HSV infections are in young children. Small treatment trials of antiviral therapy in children suggest that treatment is beneficial if begun early during primary HSV infections.[2,3] As an example, in a randomized trial of 72 children (one to six years of age) with herpes gingivostomatitis who were treated with one week of oral acyclovir (15 mg/kg up to a dose of 200 mg five times daily) or placebo within three days of illness onset, those who received acyclovir had earlier disappearance of fever (1 versus 3 days), shorter duration of lesions (median 4 versus 10 days), decreased duration of odynophagia (4 versus 7 days), and reduced viral shedding (1 versus 5 days).[2] In this trial, acyclovir was well tolerated without any significant side effects.

Dosing of antiviral therapy — Oral treatment options for adolescents and adults with primary infection include:

- Acyclovir: 400 mg orally three times daily or 200 mg five times daily

- Famciclovir: 250 mg three times daily or 500 mg twice daily
- Valacyclovir: 1 g twice daily

Most of the data evaluating the efficacy of treatment have been with acyclovir, as described above.[2,3] However, for patients who are able to tolerate oral medications, it may be preferable to use an agent such as valacyclovir, which has greater bioavailability than acyclovir, and therefore requires less frequent dosing. Dose adjustments for patients with reduced kidney function are described in the Lexicomp drug information topics within UpToDate.

Patients with severe odynophagia may sometimes require hospitalization for intravenous acyclovir therapy (5 mg/kg dosed every eight hours in patients with normal renal function) and intravenous fluids. Such patients can be transitioned to oral therapy to complete the course of treatment when they are able to comfortably swallow.

The usual duration of treatment is 7 to 10 days, depending on the severity of symptoms and response to therapy. If the lesions have not healed or progressed to the dry crust phase after 10 days, the duration of treatment can be extended.

Dosing recommendations for first-episode oral or genital HSV-1 infection are extrapolated from the treatments studied for primary genital HSV-2 infection.[4] (See "Treatment of genital herpes simplex virus infection", section on 'Treatment of first episode'.)

Adjuvant therapy — Patients who present with gingivostomatitis often require either topical or oral administration of analgesics. As an example, short-term pain relief can be achieved via mouth rinses with viscous lidocaine or topical benzocaine. Intravenous rehydration may be required for patients with severe odynophagia.

Recurrent infections — Oral HSV-1 recurrences occur when the virus reactivates from the trigeminal sensory ganglion, where it persists in a latent state. Symptomatic reactivation leads to oral herpes ("cold sores"), which occur along the vermillion border of the lips.Recurrent mucosal HSV-1 infections are generally associated with less severe clinical symptoms and a shorter duration of illness than primary disease. Some patients recognize that reactivation of disease is about to occur due to the onset of prodromal symptoms (eg, pain, tingling, burning), which precede the development of vesicles. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection".)

Various strategies may be employed in the management of patients with HSV-1 reactivation disease. These include:

- No treatment
- Episodic therapy
- Chronic suppressive therapy

Choosing a strategy should be done on a case-by-case basis, taking into account the severity of symptoms, the frequency of recurrences, the presence of a well-defined prodrome, patient preference, and cost.[5]

Patients with mild to moderate symptoms — Many patients experience occasional clinical recurrences with minimal symptoms, and in such patients antiviral treatment may not be necessary. To help alleviate the minor discomfort, treatment options include symptomatic relief with local anesthetics, such as topical lidocaine.

However, for patients who have occasional recurrences that are more severe, particularly those with a well-defined prodrome, we suggest episodic oral antiviral therapy, since treatment can decrease the length of recurrences if initiated promptly after onset.[6] Patients should have medications readily available so they can initiate therapy as soon as symptoms start to develop (eg, during the prodromal period). Episodic treatment must be initiated quickly to be effective, given the rapid development of vesicles once prodromal symptoms occur and the rapid decline in viral shedding during reactivation disease (< 48 hours).

The choice of oral agents includes:

- Acyclovir (400 mg three times daily for five days)
- Famciclovir (750 mg twice daily for one day or 1 500 mg as a single dose)
- Valacyclovir (2 g twice daily for one day)

Dose adjustments for patients with reduced kidney function are described in the Lexicomp drug information topics within UpToDate.

There are no clinical trials directly comparing any of these antiviral agents for oral HSV;[7] however, high-dose, single-day dosing with either famciclovir or valacyclovir affords greater patient convenience compared with acyclovir.[8]

Placebo-controlled trials have demonstrated that oral antiviral therapy with acyclovir, famciclovir, or valacyclovir hastens the healing of lesions by approximately one to two days if treatment is initiated during the prodromal stage:

- In one trial, 174 immunocompetent subjects with recurrent oral herpes were randomly assigned to oral acyclovir (400 mg taken five times daily for five days) versus placebo within one hour of onset of prodromal symptoms.[9] The acyclovir group had a decreased frequency of HSV culture-positive lesions (25 versus 48 percent). Treatment decreased the duration of the lesions that did occur by approximately 2.1 days compared with placebo.
- In a randomized, double-blind trial, 701 patients with recurrent herpes labialis were randomly assigned to placebo or famciclovir (as a single dose of 1 500 mg or 750 mg twice daily for a single day).[10] All were instructed to take their assigned treatment within one hour of onset of prodromal symptoms. The time to healing of lesions was significantly shorter in the two treatment groups (4.4 and 4.0 days) compared with placebo (6.2 days).
- Two randomized trials compared short-course regimens of valacyclovir administered for prodromal symptoms for one day (2 g twice daily) or two days (2 g twice daily on the first day and 1 g twice daily on the second day).[11] Valacyclovir shortened outbreaks by approximately one day compared with placebo;

treatment for one day was as effective as treatment for two days.

We do not use topical antivirals, since topical therapy must be administered multiple times per day and is less effective than oral antiviral therapy. Many of the topical agents are based on acyclovir or related compounds (eg, penciclovir) as the active component.[12,13] One of the largest randomized trials assigned 1 573 patients with frequent recurrences of oral HSV-1 infection to receive penciclovir cream or placebo every two hours during the day for four days.[12] The penciclovir cream modestly decreased the time to lesion healing (4.8 versus 5.5 days), the duration of pain (3.5 versus 4.1 days), and viral shedding. Studies have also evaluated topical agents unrelated to acyclovir that are available over the counter in the United States (eg, benzalkonium chloride-benzocaine [Orajel single-dose, Viroxyn], docosanol [Abreva]); however, data are conflicting regarding the potential benefit.[14-16]

Patients with severe disease — We suggest chronic suppressive antiviral therapy for certain patients to reduce the number of clinical HSV episodes.[17,18] This includes those who have any of the following:

- Frequent recurrences of oral HSV-1, particularly if there is no clear prodrome
- Recurrences that are very bothersome to the patient (eg, disfiguring lesions or lesions associated with severe pain)
- Recurrences that are associated with serious systemic complications (eg, erythema multiforme)[19,20] (see 'Cutaneous disease' below)

We initiate suppressive therapy with acyclovir (400 mg orally twice daily) or valacyclovir (500 mg orally once daily). The dose of valacyclovir can be increased to 1 g daily for those with breakthrough recurrences. Dose adjustments for patients with reduced kidney function are described in the Lexicomp drug information topics within UpToDate. Long-term use of these agents appears safe,[21-23] and specific laboratory monitoring on treatment is not recommended.

The need to continue suppressive therapy should be evaluated annually; however, patients should be counseled that episodes may recur once the antivirals are stopped.[24]

Studies demonstrating a benefit of chronic suppressive therapy include:

- In a controlled trial, 56 adults with a history of frequently recurrent herpes labialis (six or more episodes/year) were observed during a four-month period; 22 patients who had two or more episodes of herpes labialis were randomly assigned to receive either acyclovir (400 mg twice daily) or matched placebo. After the first treatment period, patients were switched to the alternate arm for another four months. Recurrent outbreaks were determined by physical examination and by viral culture. The acyclovir group had a lower mean number of recurrences (0.85 versus 1.8 recurrences) and a longer median time to their first documented recurrence (118 versus 46 days).[17]
- Two small randomized, double-blind trials evaluated oral valacyclovir (500 mg once daily) versus placebo for 16 weeks in patients with frequent recurrences or herpes labialis (four or more episodes during the previous year).[18] Patients receiving valacyclovir were more likely to remain free of recurrences during the four-month period than those receiving placebo (60 versus 38 percent). The time to the first recurrence was significantly longer with antiviral therapy (13 versus 9.6 weeks).

There are no studies directly comparing acyclovir and valacyclovir, and there are no data on the use of famciclovir to suppress oral HSV recurrences.

Genital infections — Patients with primary genital HSV-1 typically present with bilateral genital ulcerations and tender lymphadenopathy. Systemic symptoms such as fevers, headache, and myalgias can also occur. Genital HSV-1 lesions may recur, particularly in the first year after infection; however, multiple recurrences are rare in the setting of HSV-1 infection. The treatment of genital herpes is similar to that or oral disease and is discussed elsewhere. (See "Treatment of genital herpes simplex virus infection" and "Genital herpes simplex virus infection and pregnancy".)

Other HSV-1 infections — In immunocompetent patients, primary and recurrent HSV-1 infections can occur at a variety of anatomic sites, such as the genital tract, skin, eye, and central nervous system, although these occur less frequently than herpes gingivostomatitis and labialis. On rare occasion, disseminated disease involving visceral organs, such as the liver and spleen, can also be seen.[25] (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Clinical manifestations'.)

Cutaneous disease — HSV-1 can cause cutaneous skin lesions in a patient with primary HSV infection. These include herpetic whitlow, herpes gladiatorum, eczema herpeticum, and erythema multiforme. The etiology of these skins infections is thought to be due to autoinoculation from mucocutaneous lesions or through primary inoculation of the skin during viremia. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Cutaneous manifestations'.)

There are no formal studies evaluating treatment of skin infections due to HSV-1 infection, and the approach depends upon the specific condition. As examples:

- For most patients with cutaneous disease, we initiate oral therapy using the same dosing and duration as those used for the treatment of primary gingivostomatitis or pharyngitis.[26] (See 'Dosing of antiviral therapy' above.)

  In contrast, for hospitalized burn patients with vesicular lesions, we initiate treatment with intravenous acyclovir administered at doses also adequate to treat varicella-zoster virus (eg, 10 mg/kg every eight hours in patients with normal renal function) until cultures confirm cutaneous HSV-1 infection; then dosing can be reduced to 5 mg/kg every eight hours.[27] Once the patient is substantially improved,

with crusting of all lesions, they can be transitioned to oral antivirals to complete the course. Although HSV-1 infection can be very severe in burn patients, we do not administer prophylactic antiviral therapy; however, early recognition and treatment with acyclovir are important.[27]

- For some patients with frequent recurrences, suppressive therapy may be warranted using the same regimens as those used to suppress recurrent oral disease. (See 'Patients with severe disease' above.)

  Suppressive therapy may be particularly important for those with erythema multiforme felt to be triggered by HSV. (See "Erythema multiforme: Management", section on 'Herpes simplex virus-induced or idiopathic erythema multiforme'.)

Disseminated or visceral disease — Primary HSV-1 infection may rarely lead to widespread vesicular eruptions in the immunocompetent host or visceral disease (eg, hepatitis) with or without skin lesions.[28] Visceral disease may be associated with high morbidity and mortality, and, therefore, early diagnosis and prompt initiation of intravenous acyclovir are critical. Disseminated disease, often with prominent hepatitis, is important to consider in the differential diagnosis of pregnant people with hepatitis. (See "Overview of coincident acute hepatobiliary disease in pregnant women", section on 'Herpes simplex hepatitis'.)

Patients with disseminated or visceral disease should receive intravenous acyclovir (5 mg/kg every eight hours in patients with normal renal function).[29] Such patients should be managed in consultation with an infectious disease specialist, if possible. The duration of treatment is unclear and depends upon the patient's response to therapy (eg, clinical response, normalization of liver function tests, clearance of viremia).

Ocular infections — HSV keratitis (corneal infection and inflammation) is a major cause of blindness from corneal scarring and opacity worldwide. The treatment of HSV keratitis is discussed elsewhere. (See "Herpes simplex keratitis".)

Central nervous system disease — HSV-1 is the most common cause of acute, nonepidemic viral encephalitis in the United States. HSV-1 is also an etiologic agent of Bell's palsy.[30] The treatment of these clinical entities is discussed separately. (See "Herpes simplex virus type 1 encephalitis" and "Bell's palsy: Treatment and prognosis in adults".)

Future drug development — Two helicase-primase inhibitors have shown activity against HSV-1 and HSV-2 in animal models.[31,32] In human trials, these candidate agents have antiviral activity, but safety concerns have led to a halt in further development for use in oral or genital herpes.[33,34] Pritelivir is being studied in a Phase 3 clinical trial for acyclovir- resistant herpes in immunocompromised hosts (clinicaltrials.gov NCT03073967).

Prophylaxis for recurrent HSV with identified trigger

Both iatrogenic and natural triggers can lead to predictable HSV-1 infections in some patients.[35-39] Treatment trials have addressed a variety of strategies when managing these patients.

Sunlight exposure — In some patients, intense sunlight exposure can lead to HSV-1 reactivation.[35,36] Various treatment strategies have been evaluated to prevent these recurrences, including zinc-based sunscreen products and topical and oral antiviral therapies, although no studies have directly compared any of these strategies.

We advise patients with HSV-1 triggered by sunlight to use sunscreen. A placebo-controlled crossover trial of 38 patients found that after ultraviolet (UV) light exposure, herpes labialis developed in 27 patients (71 percent) treated with placebo with a mean time to HSV recurrence of 2.9 days.[40] In contrast, when sunscreen was applied before UV light exposure, no lesions developed, although 1 of 35 patients did shed virus at the UV light exposure site.

In general, we suggest **not** using prophylactic antiviral therapy for the sole purpose of preventing recurrences due to sunlight, since there are conflicting data on the benefit of antiviral therapy in this setting. However, some patients with frequent recurrences may choose to go on suppressive therapy, as discussed above. (See 'Patients with severe disease' above.)

Studies evaluating the use of oral therapy to prevent reactivation in the setting of sun exposure include:

- A randomized trial was performed among 237 skiers with a history of recurrent labial herpes triggered by sun exposure to determine if acyclovir could lead to a lower frequency of HSV reactivation or faster lesion resolution.[35] Oral acyclovir (800 mg twice daily) was initiated 12 to 24 hours before sun exposure and continued for three to seven days. Patients in the treatment arm did not have any clinical benefit compared with those in the placebo arm.
- In another trial, 147 skiers with a history of sun-induced recurrences of HSV-1 were treated prophylactically with oral acyclovir (400 mg twice daily) or matching placebo and were observed during their ski holidays.[41] This study demonstrated a clinical benefit of acyclovir prophylaxis; 5 (7 percent) of 75 acyclovir-treated subjects developed lesions compared with 19 (26 percent) of 72 persons in the placebo group.
- A systematic review and meta-analysis of studies that examined the effectiveness of topical and systemic antivirals in the prevention of oral herpes found that both oral acyclovir (800 to 1 600 mg daily) and valacyclovir (500 mg daily) were effective in reducing the risk of oral herpes when initiated prior to exposure to triggers.[42]

Similarly, placebo-controlled trials of topical antiviral creams have shown conflicting results as to whether treatment decreases the risk of recurrence in patients with light-induced herpes labialis.[43-45]

Surgical procedures — HSV reactivation can be seen in the setting of surgical procedures, such as trigeminal nerve root decompression, facial dermabrasion, and ablative laser resurfacing;[46-53] in some reports, the risk of recurrent oral herpes has been reported to be as high as 50 to 70 percent. Given the high risk of HSV reactivation associated with these procedures, we typically administer antiviral prophylaxis around the time of surgery, even to those without a known history of HSV.

There are no standardized regimens, so we typically use those that have been described in studies evaluating the efficacy of antiviral prophylaxis in these settings. As examples:

- Trigeminal surgery – For patients undergoing trigeminal surgery, we administer oral acyclovir (400 mg twice daily) starting the night before surgery and continuing twice daily for five days. In a controlled trial of 30 patients, this regimen led to a high degree of protection against HSV reactivation compared with placebo (1 versus 12 patients developed herpes labialis).[45,54] In addition, at day 3 after surgery, HSV-positive cultures were demonstrated in 3 of 14 patients in the treatment arm versus 12 of 16 placebo recipients. Prior oral herpes infection or presence of antibodies to HSV was not required for participation in the trial, and only 13 (43 percent) had a history of herpes labialis.
- Dermabrasion – For patients undergoing dermabrasion, we administer valacyclovir (500 mg twice daily) for 14 days. There ere no episodes of HSV reactivation in 84 patients undergoing dermabrasion over a 21-day period of observation when this regimen was initiated the morning before or the morning of the procedure;[55] however, the study did not include a placebo arm for comparison, and only 70 percent of participants in the study had HSV-1 antibodies.
- Ablative laser resurfacing – For ablative laser resurfacing, acyclovir, valacyclovir, or famciclovir can be used.[46] Regimens for oral prophylaxis in this setting are discussed elsewhere. (See "Ablative laser resurfacing for skin rejuvenation", section on 'Prophylaxis'.)

Dose adjustments of these agents for patients with reduced kidney function are described in the Lexicomp drug information topics within UpToDate.

HSV reactivation has been occasionally reported in patients undergoing dental extractions,[56,57] and there are conflicting data as to whether dental surgery leads to an increase in asymptomatic HSV shedding;[58,59] however, routine antiviral prophylaxis is not recommended for these procedures.

Preventing new HSV-1 infections

Most HSV-1 infections are acquired during intimate (but not necessarily sexual) contact. Family members are the most likely source, but others may be a source when saliva-sharing behavior occurs.

Although there are no licensed vaccines to prevent HSV-1 infection,[60] certain strategies may help reduce the risk of transmitting HSV-1 to someone without prior infection. As an example, when a patient has an active outbreak of oral HSV, patients should avoid kissing or sharing utensils, glasses, water bottles, towels, or lip balm. Although this may not reduce the risk completely, since asymptomatic shedding can occur, transmission is most likely in the setting of active lesions. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Transmission'.)

Other strategies may also reduce the risk of transmission in select settings. Examples include:

- **Health care workers** – To prevent acquisition of HSV infection, health care workers should use gloves during physical examination of a patient with active HSV lesions and for examination of mucus membranes. Providers involved with procedures that may involve exposure to infected secretions, such as suctioning or bronchoscopy, should also wear eye and mouth protection.
- **Sexual transmission** – Patients with oral HSV infection (primary or recurrent) should be educated that they can transmit HSV-1 through oral sex to uninfected partners, which may result in genital ulcers.[61] This issue is particularly important if the HSV-negative partner is pregnant, given that HSV acquisition during pregnancy is associated with high risk for transmission to the neonate.[62] (See "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection" and "Genital herpes simplex virus infection and pregnancy".)

  To reduce the risk of transmission, barrier use for oral sex is recommended.[63] Whether condom use is effective against sexual transmission of genital-to-genital HSV-1 has not been evaluated; however, extrapolating from HSV-2 data, it is likely that condoms reduce the risk of transmission when HSV shedding is present. Studies of condom effectiveness for genital HSV-2 indicate substantial protection for men and a high level of protection for women whose partners used condoms.[64] (See "Prevention of sexually transmitted infections".)

  The decision to use valacyclovir to prevent sexual transmission of HSV-1 to an uninfected partner must be determined using shared decision making with the patient. Although valacyclovir is effective in reducing the risk of transmission of genital HSV-2 infection in heterosexual, discordant couples,[65] its role in the prevention of sexual transmission of HSV-1 infection has not been studied. (See "Prevention of genital herpes virus infections".)
- **Herpes gladiatorum** – Cutaneous HSV-1 infections are common among certain athletes, such as wrestlers. To prevent transmission to others, athletes should not participate in contact sports until all herpes lesions have entered the dry crust stage. In addition, the use of suppressive oral antiviral therapy in those with and without a known history of HSV-1 may reduce the risk of an outbreak in certain settings by reducing both the risk for transmission and acquisition. As an example, one summer camp suggested all wrestlers, regardless of their history of HSV, take prophylactic valacyclovir (1 g once

daily) while at the camp, and this resulted in an 85 percent decrease in the likelihood of developing an outbreak.[66]

Summary and recommendations

- **Spectrum of disease** – Herpes simplex virus type 1 (HSV-1) can cause recurrent vesiculoulcerative lesions of the oral or genital mucosa. It can also cause infection in the eye, skin, central nervous system, and visceral organs. (See 'Introduction' above.)
- **Antiviral agents** – Antiviral agents for HSV infection include acyclovir, valacyclovir, and famciclovir; metabolites of these nucleoside derivatives interfere with the synthesis of viral DNA and are well tolerated. With all of these agents, dose adjustment is needed in patients with moderate to severe renal insufficiency, since acyclovir and its analogues are dependent upon renal function for clearance. (See 'General principles' above.)
- **Treatment of primary oral infection** – For most patients with gingivostomatitis or pharyngitis due to primary HSV infection, we recommend antiviral therapy within 72 hours of symptom onset (**Grade 1B**). Early antiviral therapy leads to earlier healing of lesions, decreased pain, and a shorter duration of fever. However, if a patient presents after this time frame with ongoing development of lesions and/or significant pain, antiviral therapy should still be offered. (See 'Primary infection' above and 'Whom to treat' above.)
  - Treatment of primary HSV gingivostomatitis or pharyngitis typically consists of oral therapy with acyclovir (eg, 400 mg three times daily), famciclovir (eg, 500 mg twice daily), or valacyclovir (1 g twice daily) for 7 to 10 days.
  - Patients with severe odynophagia may sometimes require hospitalization for intravenous acyclovir therapy and intravenous fluids. Such patients can be transitioned to oral therapy when they can comfortably swallow. (See 'Primary infection' above and 'Dosing of antiviral therapy' above.)
- **Management of recurrent oral infections** – Various strategies may be employed in the management of immunocompetent patients with recurrent oral infections (eg, cold sores), including no treatment, episodic therapy, or chronic suppressive therapy. The choice depends upon the severity of symptoms, the presence of a recognizable prodrome, and patient preference.
  - Many patients experience occasional clinical recurrences with minimal symptoms and, in such patients, treatment may not be necessary. To help alleviate the minor discomfort, treatment options include symptomatic relief with local anesthetics and antiseptics. (See 'Patients with mild to moderate symptoms' above.)
  - For patients who have occasional recurrences that are more severe and have an identifiable prodrome, we suggest episodic oral antiviral therapy (**Grade 2B**). Treatment can decrease the length of recurrences if initiated promptly after symptom onset (eg, during the prodrome). We do not use topical antiviral therapy since it must be administered multiple times per day and is less effective than oral antivirals. (See 'Patients with mild to moderate symptoms' above.)
  - For patients with frequent, painful, or disfiguring lesions, particularly those who do not have an identifiable prodrome, we suggest chronic suppressive therapy rather than episodic therapy (**Grade 2C**). Chronic suppressive therapy is also well suited for patients who have HSV recurrences associated with serious complications (eg, erythema multiforme). (See 'Patients with severe disease' above.)
  - Some patients will have an identifiable trigger for developing recurrent disease, and interventions may reduce the risk of HSV-1 in this setting. As an example, when sun exposure is identified as a potential trigger, use of sunscreen may help prevent a recurrence.

    Prophylactic oral therapy may prevent HSV reactivation during certain procedures, such as trigeminal nerve root decompression, facial dermabrasion, or ablative laser resurfacing. (See 'Prophylaxis for recurrent HSV with identified trigger' above.)
- **Management of non-oral infections** – For patients who develop HSV-1 infection at other anatomic sites (eg, the genital tract, skin, eye, or central nervous system), or who develop disseminated disease involving visceral organs, the approach to treatment depends upon the specific manifestation. Although oral therapy is used to treat most of these infections, intravenous therapy is usually indicated for more severe disease (eg, hepatitis, encephalitis). (See 'Genital infections' above and 'Other HSV-1 infections' above.)
- **Reducing risk of transmission** – Patients with HSV-1 infection should be educated about how HSV-1 is transmitted and provided with strategies to reduce the risk of transmitting virus to others (eg, avoid sharing utensils, glasses, or water bottles, particularly when patient has active lesions). They should also be reminded that HSV-1 can be transmitted to uninfected partners through oral sex, which may result in genital infections. (See 'Preventing new HSV-1 infections' above.)

Acknowledgment

The UpToDate editorial staff acknowledges Robyn S Klein, MD, PhD, who contributed to an earlier version of this topic review.

Contributor Disclosures

Anna Wald, MD, MPH Grant/Research/Clinical Trial Support: GlaxoSmithKline [HSV therapeutic vaccine]. Consultant/Advisory Boards: AiCuris [HSV novel antiviral]; Curevo [Novel VZV vaccine]. All of the relevant financial relationships listed have been mitigated. **Christine Johnston, MD, MPH** Grant/Research/Clinical Trial Support: GSK [HSV]; Moderna [HSV]. Consultant/Advisory Boards: Assembly Biosciences [HSV]; GSK [HSV]. Other Financial Interest: Gilead [HSV and Alzheimer's Disease, contracted research]. All of the relevant financial relationships listed have been mitigated. **Martin S Hirsch, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Jennifer Mitty, MD, MPH** No

relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

References

1. De Clercq E. Selective anti-herpesvirus agents. Antivir Chem Chemother 2013; 23:93.
2. Amir J, Harel L, Smetana Z, Varsano I. Treatment of herpes simplex gingivostomatitis with aciclovir in children: a randomised double blind placebo controlled study. BMJ 1997; 314:1800.
3. Ducoulombier H, Cousin J, Dewilde A, et al. [Herpetic stomatitis-gingivitis in children: controlled trial of acyclovir versus placebo]. Ann Pediatr (Paris) 1988; 35:212.
4. Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021; 70:1.
5. Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections: an evidence- based review. Arch Intern Med 2008; 168:1137.
6. Gilbert SC. Management and prevention of recurrent herpes labialis in immunocompetent patients. Herpes 2007; 14:56.
7. Jensen LA, Hoehns JD, Squires CL. Oral antivirals for the acute treatment of recurrent herpes labialis. Ann Pharmacother 2004; 38:705.
8. Valacyclovir (valtrex) for herpes labialis. Med Lett Drugs Ther 2002; 44:95.
9. Spruance SL, Stewart JC, Rowe NH, et al. Treatment of recurrent herpes simplex labialis with oral acyclovir. J Infect Dis 1990; 161:185.
10. Spruance SL, Bodsworth N, Resnick H, 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.
11. Spruance SL, Jones TM, Blatter MM, et al. High-dose, short-duration, early valacyclovir therapy for episodic treatment of cold sores: results of two randomized, placebo- controlled, multicenter studies. Antimicrob Agents Chemother 2003; 47:1072.
12. Spruance SL, Rea TL, Thoming C, et al. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. Topical Penciclovir Collaborative Study Group. JAMA 1997; 277:1374.
13. Spruance SL, Nett R, Marbury T, et al. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. Antimicrob Agents Chemother 2002; 46:2238.
14. McKeough MB, Spruance SL. Comparison of new topical treatments for herpes labialis: efficacy of penciclovir cream, acyclovir cream, and n-docosanol cream against experimental cutaneous herpes simplex virus type 1 infection. Arch Dermatol 2001; 137:1153.
15. Sacks SL, Thisted RA, Jones TM, et al. Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: A multicenter, randomized, placebo-controlled trial. J Am Acad Dermatol 2001; 45:222.
16. McCarthy JP, Browning WD, Teerlink C, Veit G. Treatment of herpes labialis: comparison of two OTC drugs and untreated controls. J Esthet Restor Dent 2012; 24:103.
17. Rooney JF, Straus SE, Mannix ML, et al. Oral acyclovir to suppress frequently recurrent herpes labialis. A double-blind, placebo-controlled trial. Ann Intern Med 1993; 118:268.
18. Baker D, Eisen D. Valacyclovir for prevention of recurrent herpes labialis: 2 double-blind, placebo-controlled studies. Cutis 2003; 71:239.
19. Vestey JP, Norval M. Mucocutaneous infections with herpes simplex virus and their management. Clin Exp Dermatol 1992; 17:221.
20. Green JA, Spruance SL, Wenerstrom G, Piepkorn MW. Post-herpetic erythema multiforme prevented with prophylactic oral acyclovir. Ann Intern Med 1985; 102:632.
21. Worrall G. Acyclovir in recurrent herpes labialis. BMJ 1996; 312:6.
22. Lebrun-Vignes B, Bouzamondo A, Dupuy A, et al. A meta-analysis to assess the efficacy of oral antiviral treatment to prevent genital herpes outbreaks. J Am Acad Dermatol 2007; 57:238.
23. Fife KH, Crumpacker CS, Mertz GJ, et al. Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years of chronic suppression with acyclovir. Acyclovir Study Group. J Infect Dis 1994; 169:1338.
24. Nikkels AF, Pièrard GE. Treatment of mucocutaneous presentations of herpes simplex virus infections. Am J Clin Dermatol 2002; 3:475.
25. Arduino PG, Porter SR. Herpes Simplex Virus Type 1 infection: overview on relevant clinico-pathological features. J Oral Pathol Med 2008; 37:107.
26. Kesson AM. Use of aciclovir in herpes simplex virus infections. J Paediatr Child Health 1998; 34:9.
27. Fidler PE, Mackool BT, Schoenfeld DA, et al. Incidence, outcome, and long-term consequences of herpes simplex virus type 1 reactivation presenting as a facial rash in intubated adult burn patients treated with acyclovir. J Trauma 2002; 53:86.
28. Moedy JL, Lerman SJ, White RJ. Fatal disseminated herpes simplex virus infection in a healthy child. Am J Dis Child 1981; 135:45.
29. Mantry P, Desai D, Kumar V, Udwadia T. Herpes simplex hepatitis. Indian J Gastroenterol 1997; 16:33.
30. Furuta Y, Fukuda S, Chida E, et al. Reactivation of herpes simplex virus type 1 in patients with Bell's palsy. J Med Virol 1998; 54:162.
31. Crute JJ, Grygon CA, Hargrave KD, et al. Herpes simplex virus helicase-primase inhibitors are active in animal models of human disease. Nat Med 2002; 8:386.
32. Kleymann G, Fischer R, Betz UA, et al. New helicase-primase inhibitors as drug candidates for the treatment of herpes simplex disease. Nat Med 2002; 8:392.
33. Wald A, Timmler B, Magaret A, et al. Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences: A Randomized Clinical Trial. JAMA 2016; 316:2495.
34. Tyring S, Wald A, Zadeikis N, et al. ASP2151 for the treatment of genital herpes: a randomized, double-blind, placebo- and valacyclovir-controlled, dose-finding study. J Infect Dis 2012; 205:1100.
35. Raborn GW, Martel AY, Grace MG, McGaw WT. Oral acyclovir in prevention of herpes labialis. A randomized, double-blind, multi-centered clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 85:55.
36. Spruance SL, Rowe NH, Raborn GW, et al. Peroral famciclovir in the treatment of experimental ultraviolet radiation-induced herpes simplex labialis: A double-blind, dose- ranging, placebo-controlled, multicenter trial. J Infect Dis 1999; 179:303.
37. Spruance SL, Freeman DJ, Stewart JC, et al. The natural history of ultraviolet radiation- induced herpes simplex labialis and response to therapy with peroral and topical formulations of acyclovir. J Infect Dis 1991; 163:728.
38. Gilbert SC. Suppressive therapy versus episodic therapy with oral valacyclovir for recurrent herpes labialis: efficacy and tolerability in an open-label, crossover study. J Drugs Dermatol 2007; 6:400.
39. Mills J, Hauer L, Gottlieb A, et al. Recurrent herpes labialis in skiers. Clinical observations and effect of sunscreen. Am J Sports Med 1987; 15:76.
40. Rooney JF, Bryson Y, Mannix ML, et al. Prevention of ultraviolet-light-induced herpes labialis by sunscreen. Lancet 1991; 338:1419.
41. Spruance SL, Hamill ML, Hoge WS, et al. Acyclovir prevents reactivation of herpes simplex labialis in skiers. JAMA 1988; 260:1597.
42. Rahimi H, Mara T, Costella J, et al. Effectiveness of antiviral agents for the prevention of recurrent herpes labialis: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2012; 113:618.
43. Evans TG, Bernstein DI, Raborn GW, et al. Double-blind, randomized, placebo-controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced herpes labialis. Antimicrob Agents Chemother 2002; 46:1870.
44. Bernstein DI, Schleupner CJ, Evans TG, et al. Effect of foscarnet cream on experimental UV radiation-induced herpes labialis. Antimicrob Agents Chemother 1997; 41:1961.
45. Chi CC, Wang SH, Delamere FM, et al. Interventions for prevention of herpes simplex labialis (cold sores on the lips). Cochrane Database Syst Rev 2015; :CD010095.
46. Wall SH, Ramey SJ, Wall F. Famciclovir as antiviral prophylaxis in laser resurfacing procedures. Plast Reconstr Surg 1999; 104:1103.
47. Alster TS, Nanni CA. Famciclovir prophylaxis of herpes simplex virus reactivation after laser skin resurfacing. Dermatol Surg 1999; 25:242.

48. Whitley RJ, Gnann JW Jr. Acyclovir: a decade later. N Engl J Med 1992; 327:782.
49. Metelitsa AI, Alster TS. Fractionated laser skin resurfacing treatment complications: a review. Dermatol Surg 2010; 36:299.
50. Berra LV, Armocida D, Pesce A, et al. Herpes Simplex Reactivation After Surgical Treatment of Trigeminal Neuralgia: A Retrospective Cohort Study. World Neurosurg 2019; 127:e16.
51. Tenser RB. Occurrence of Herpes Simplex Virus Reactivation Suggests a Mechanism of Trigeminal Neuralgia Surgical Efficacy. World Neurosurg 2015; 84:279.
52. Pazin GJ, Ho M, Jannetta PJ. Reactivation of herpes simplex virus after decompression of the trigeminal nerve root. J Infect Dis 1978; 138:405.
53. Silverman AK, Laing KF, Swanson NA, Schaberg DR. Activation of herpes simplex following dermabrasion. Report of a patient successfully treated with intravenous acyclovir and brief review of the literature. J Am Acad Dermatol 1985; 13:103.
54. Schädelin J, Schilt HU, Rohner M. Preventive therapy of herpes labialis associated with trigeminal surgery. Am J Med 1988; 85:46.
55. Gilbert S, McBurney E. Use of valacyclovir for herpes simplex virus-1 (HSV-1) prophylaxis after facial resurfacing: A randomized clinical trial of dosing regimens. Dermatol Surg 2000; 26:50.
56. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. Arch Intern Med 2009; 169:1233.
57. Openshaw H, Bennett HE. Recurrence of herpes simplex virus after dental extraction. J Infect Dis 1982; 146:707.
58. Hyland PL, Coulter WA, Abu-Ruman I, et al. Asymptomatic shedding of HSV-1 in patients undergoing oral surgical procedures and attending for noninvasive treatment. Oral Dis 2007; 13:414.
59. Marques-Silva L, Castro WH, Gomez EL, et al. The impact of dental surgery on HSV-1 reactivation in the oral mucosa of seropositive patients. J Oral Maxillofac Surg 2007; 65:2269.
60. Whitley RJ, Roizman B. Herpes simplex viruses: is a vaccine tenable? J Clin Invest 2002; 110:145.
61. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis 2003; 30:797.
62. Brown ZA, Benedetti J, Ashley R, 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.
63. Delaney S, Gardella C, Daruthayan C, et al. A prospective cohort study of partner testing for herpes simplex virus and sexual behavior during pregnancy. J Infect Dis 2012; 206:486.
64. Magaret AS, Mujugira A, Hughes JP, et al. Effect of Condom Use on Per-act HSV-2 Transmission Risk in HIV-1, HSV-2-discordant Couples. Clin Infect Dis 2016; 62:456.
65. 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.
66. Anderson BJ, McGuire DP, Reed M, et al. Prophylactic Valacyclovir to Prevent Outbreaks of Primary Herpes Gladiatorum at a 28-Day Wrestling Camp: A 10-Year Review. Clin J Sport Med 2016; 26:272.