REVIEW ARTICLE

The Treatment of Herpes Simplex Infections

An Evidence-Based Review

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Genital and labial herpes simplex virus infections are frequently encountered by primary care physicians in the United States. Whereas the diagnosis of this condition is often straightforward, choosing an appropriate drug (eg, acyclovir, valacyclovir hydrochloride, or famciclovir) and dosing regimen can be confusing in view of (1) competing clinical approaches to therapy; (2) evolving dosing schedules based on new research; (3) approved regimens of the Food and Drug Administration that may not match recommendations of the Centers for Disease Control and Prevention or of other experts; and (4) dissimilar regimens for oral and genital infections. The physician must first choose an approach to treatment (ie, intermittent episodic therapy, intermittent suppressive therapy, or chronic suppressive therapy) based on defined clinical characteristics and patient preference. Then, an evidence-based dosing regimen must be selected. In this review, data from all sources are tabulated to provide a handy clinical reference. *Arch Intern Med. 2008;168(11):1137-1144*

Acyclovir, valacyclovir hydrochloride, and famciclovir are the 3 antiviral drugs routinely used to treat symptomatic herpes simplex virus (HSV) infections. Diagnosing HSV infections is usually straightforward in immunocompetent patients, and all the available drugs have an excellent margin of safety because they are converted by viral thymidine kinase to the active drug only inside virally infected cells. Unfortunately, confusion often arises because various dosing regimens are recommended for (1) each of the 3 available drugs; (2) HSV vs herpes zoster; (3) suppressive vs intermittent episodic indications; (4) primary vs secondary infections; (5) oral and genital infections; and (6) evolving treatment strategies approved by the Food and Drug Administration. Following a literature review to document important clinical information about HSV infections, we discuss the data regarding optimal treatment regimens. Three approaches to treatment are described: intermittent episodic therapy (IET), chronic suppressive therapy (CST), and intermittent suppressive therapy (IST).

An outbreak of genital or labial herpes is categorized as a primary HSV infection if the patient was seronegative for HSV types 1 and 2 before the episode and as a nonprimary HSV infection if previous infections had occurred. Without acquired immunity, initial primary infections are generally more severe than recurrences. Constitutional symptoms such as fever, chills, fatigue, and muscle aches accompany the disease and last 10 to 14 days. A first episode of genital or oral herpes in a patient already seropositive for HSV is termed a nonprimary initial infection, and these infections tend to be less severe. The disease course after initial infection is variable; some patients have recurrent infections, and others never experience a second episode.

Labial herpes typically results from infection with HSV type 1 and is commonly contracted during childhood or adolescence. In the US, 57% to 80% of

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Figure. Grouped vesicopustules are present on the right side of the chin just below the vermillion border 48 hours after the patient first noted tingling and burning at this site. This is the 25th recurrence at this site in 10 years.

Table 1. Episodic Dosing for Initial Primary Labial Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved
Acyclovir	15 mg/kg 5 times a day for 7 d	II[3,21]	No
Valacyclovir hydrochloride	1 g twice a day for 7 d	V[22]	No
Famciclovir	500 mg twice a day for 7 d	V[22]	No

Abbreviation: FDA, Food and Drug Administration.

adults are seropositive for the virus, with a larger proportion of these people being of lower socioeconomic status.[1-4] Many people exposed to HSV demonstrate asymptomatic seroconversion. Initial primary episodes, however, can be severe, causing widespread 1- to 2-mm blisters associated with severe discomfort that interferes with eating and drinking to the point of dehydration, last 10 to 14 days, and occur 1 to 26 days after inoculation.[4] Recurrent labial herpes affects roughly one third of the US population, and these patients typically experience 1 to 6 episodes per year.[5-9] These infections appear at the vermillion border of the lip in about 90% of cases, the palate in 5% of cases, and elsewhere above the chin or on the oral mucosa more rarely (**Figure**). Papules on an erythematous base become vesicles within hours and subsequently progress through ulcerated, crusted, and healing stages within 72 to 96 hours.[10,11] Before skin lesions appear, 60% of patients experience the prodromes tingling, itching, and burning.[11]

Genital herpes is most commonly contracted between the ages of 15 and 30 years, coinciding with increased sexual activity in this age group.[12] It affects approximately 22% of the US population, with roughly 38% of symptomatic individuals experiencing 6 or more recurrences per year.[13,14] Genital herpes can result from infection with either HSV type 2 or type 1, mainly HSV type 2 in this country, which typically causes more recurrent and severe manifestations of disease.[2,15,16] Infection of the cervix, often subclinical, is the main site of involvement in women, yet the classic clinical picture is that of painful and disfiguring vaginal and vulvar lesions.[12] Men typically develop lesions on the glans, prepuce, or shaft of the penis. The natural course of disease progression is decreased frequency and severity of recurrences over time. However, roughly a third of patients do not experience this time-dependent regression.[17]

Herpes zoster and other blistering diseases can mimic HSV infections. The diagnosis of herpes infections can be confirmed immediately by Tzanck preparation, within hours using immunofluorescence techniques, and within 48 hours using viral culture.

The clinical courses of genital herpes caused by HSV types 1 and 2 are indistinguishable. There is typically a 2- to 21-day incubation period following viral inoculation when randomly distributed vesicles clustered on a red base appear. Tiny papules develop into vesicles, which subsequently ulcerate and crust.[18] Soreness, itching, dysuria, and inguinal or femoral lymphadenopathy may accompany constitutional symptoms, and dysuria is common in women.[18,19] Untreated eruptions of genital herpes typically last longer than those of the oral variety, with a primary episode enduring for 2 to 4 weeks. Recurrent genital herpes produces localized vesicles on an erythematous base, which persist for 7 to 12 days without treatment.[19,20]

INTERMITTENT EPISODIC THERAPY

As is the case with most disease processes, HSV infections are commonly treated with the first clinical sign or symptoms. This form of intermittent treatment is termed *episodic* and focuses on management of isolated, acute episodes of a chronic, clinically silent disease. Although the treatment approaches used for oral and genital HSV infections are more similar than different, randomized controlled trials (RCT) have uniformly studied these infections separately. Therefore, dosage schedules derived from these trials are not identical.

IET in Labial Herpes Simplex

Initial Primary Infections. In moderate and severe cases, antiviral treatment is often recommended for uncomplicated episodes of primary oral herpes in healthy patients (**Table 1**).[6] Oral acyclovir suspension, 15 mg/kg 5 times daily for 1 week, significantly decreased the disease duration and the period of infectivity in children in a small RCT. Median duration of oral lesions was 4 days vs 9 days for the placebo group, and median time to negative viral cultures was 1 day vs 5 days.[21] Valacyclovir hydrochloride, 1 g twice a day for 7 days, and famciclovir, 500 mg twice a day or once a day for 7 days, are also logical regimens, although RCTs have not been performed.[3,22] Treatment is most effective when initiated promptly. However, early treatment does not appear to diminish recurrences.

Recurrent Infections. The intermittent use of an oral antiviral agent is effective in the treatment of recurrent labial herpes when initiated within 48 hours of an outbreak (**Table 2**). Randomized controlled trials have shown systemic acyclovir (400 mg 5 times daily for 5 days) decreases healing time and viral shedding and ameliorates symptoms when initiated early.[11,23] Valacyclovir, the prodrug of acyclovir, provides a 3- to 5-fold increase in bioavailability of acyclovir.[24] Two large RCTs demonstrated that single-day administration of valacyclovir

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(2 g given twice in 24 hours) significantly reduces episode duration, time to lesion healing, and time to cessation of pain and discomfort when compared with placebo. A 1-day reduction in lesion duration was documented.

Famciclovir, the oral prodrug of penciclovir, offers increased bioavailability as well as a substantially longer half-life compared with acyclovir. In an RCT, famciclovir, given as either a single 1500-mg dose or as two 750-mg doses during a 24-hour period, decreased healing time and provided symptomatic relief. Time to lesion healing and normal reepithelialization was 2 days shorter and symptom resolution was 1 day faster when compared with the control group.[10,25]

Intermittent episodic therapy with topical acyclovir and penciclovir creams have been shown to decrease lesion healing time and symptom severity in recurrent labial herpes.[11,26,27,29-32] Other studies, however, failed to prove acyclovir ointment and cream efficacious.[33,34] Overall, topical treatments do not appear to be as effective as systemic medications. For instance, famciclovir decreases lesion healing time by 2 days, efficacy that has not been demonstrated with topical therapy.[10,26,35-37]

Table 2. Intermittent Episodic Therapy or Recurrent Labial Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved
Acyclovir	400 mg 5 times a day for 5 d	II[23]	No
Valacyclovir hydrochloride	2 g twice a day for 1 d	I[24]	Yes
Famciclovir	Three 500-mg tablets as a single dose	I[10,25]	Yes
Topical therapy			
Penciclovir cream, 1%	Apply every 2 h during waking hours for 4 d	I[26-28]	Yes
Acyclovir cream, 5%	Apply 5 times a day for 4 d	I[27,29]	Yes

Abbreviation: FDA, Food and Drug Administration.

Table 3. Episodic Dosing for Initial Primary Genital Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved	CDC Recommended
Acyclovir	400 mg 3 times a day for 7-10 d	V[38-41]	No	Yes
	200 mg 5 times a day for 7-10 d	I[38,40]	Yes	Yes
Valacyclovir hydrochloride	1 g twice a day for 7-10 d	I[40]	Yes	Yes
Famciclovir	250 mg 3 times a day for 5-10 d	I[42,43]	No	Yes (10-d regimen)

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.

IET in Genital Herpes Simplex

Initial Primary Infections. Patients with primary episodes of genital herpes are effectively treated with antiviral drugs when taken within 72 hours of lesion appearance (**Table 3**). Oral and intravenous acyclovir have been used to shorten the course of primary genital herpes infections for decades. Unlike topical acyclovir, the oral form can prevent new lesion formation and modify accompanying constitutional symptoms, and does not cause local irritation on application.[38] Oral acyclovir is more practical than the intravenous route for immunocompetent patients.[38] Acyclovir (1 g to 1200 mg/d) produces results matching those of higher dosages (4 g/d). Neither regimen appears to affect the frequency or course of future genital herpes recurrences.[39]

Head-to-head trials comparing 10-day regimens of oral acyclovir (200 mg 5 times daily) and valacyclovir (1000 mg twice a day) found no statistically significant difference between the 2 in terms of disease outcome measures.[40] However, valacyclovir, when taken once or twice daily, is likely to increase compliance compared with acyclovir, which is taken 5 times a day.[40]

Similarly, an RCT comparing the efficacy of 5- and 10-day regimens of several famciclovir dosages (250 mg, 500 mg, or 750 mg 3 times a day for 5 days and 125 mg, 250 mg, or 500 mg 3 times a day for 10 days) with acyclovir (200 mg 5 times a day for 5 or 10 days) in first-episode genital herpes cases found no significant differences between the two drugs. Duration of viral shedding, median time to lesion healing, and time to symptom resolution were comparable between both treatment groups.[42,43] The 10-day treatment arm of the study demonstrated that higher doses of famciclovir (250 mg and 500 mg) were superior to the 125-mg regimen. The Centers for Disease Control and Prevention has chosen to recommend the 10-day dosing schedule, although the 5 and 10-day regimens of famciclovir (250 mg 3 times a day and all 500-mg groups) demonstrated comparable efficacy.[42,43] Famciclovir 3 times a day should enhance compliance when compared with the 5 times daily dosage of acyclovir.

Recurrent Infections. In the 1980s, oral acyclovir (200 mg 5 times daily for 5 days) was found to significantly decrease viral shedding, hasten lesion healing, and decrease the incidence of new lesion formation.[41,44,45] It was also associated with a truncated course of pain and discomfort, but had no effect on recurrences.[41,44] Abbreviated courses using higher dosages of acyclovir, 800 mg twice a day for 5 days and 3 times a day for 2 days, have proven to be as effective as earlier regimens.[46,47] Moreover, the higher dosage was effective in healing established lesions in men, even when initiated after the prodromal period.[46]

Oral valacyclovir (500 mg twice a day for 5 days and 1 g once a day for 5 days) has been shown in placebo-controlled and head-to-head studies to match acyclovir in terms of decreasing episode length, viral shedding, and healing time.[45,48] The 3-day valacyclovir regimen (500 mg twice a day) was shown to be as effective as 5 days of treatment.[49] Multiple studies have also demonstrated that valacyclovir significantly

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Table 4. Intermittent Episodic Therapy for Recurrent Genital Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved	CDC Recommended
Acyclovir	200 mg 5 times a day for 5-10 d	I[41,44,45,53]	Yes	No
	400 mg 3 times a day for 5 d	V	No	Yes
	400 mg 3 times a day for 5-10 d[a]	V	No	Yes
	800 mg twice a day for 5 d	II[46]	No	Yes
	800 mg 3 times a day for 2 d	II[47]	No	Yes
Valacyclovir hydrochloride	500 mg twice a day for 3 d	I[49]	Yes	Yes
	1 g twice a day for 5-10 d[a]	II[54]	No	Yes
	1 g once a day for 5 d	I[48]	No	Yes
Famciclovir	125 mg twice a day for 5 d	I[51,52]	No	Yes
	500 mg twice a day for 5-10 d[a]	II[55]	Yes (7-d regimen)	Yes
	1 g twice a day for 1 d	I[14]	Yes	Yes

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.
[a] For human immunodeficiency virus–positive patients, suggested regimens were derived from studies of patients with genital herpes. However, we expect these treatments to also be useful for patients with labial herpes.

decreases the duration and severity of pain and discomfort associated with genital herpes episodes.[50] There is conflicting evidence regarding the ability of valacyclovir to abort outbreaks when taken at the onset of symptoms before any lesions are apparent. Data trends and our clinical experience suggest that at least some recurrences can be aborted through this approach.[45,48,50]

In addition, varying dosages of famciclovir (125 mg, 250 mg, or 500 mg twice a day for 5 days) significantly affect the characteristics mentioned previously. No dose-dependent advantages exist between regimens. Therefore, the lowest dosage of 125 mg twice a day is recommended. Viral shedding is decreased by 1½ days and roughly leads to complete lesion healing 1 day faster than placebo. There is a 50% absolute risk reduction of developing new lesions compared with placebo, and the treatment group enjoyed at least a half-day reduction in lesion-associated pain and discomfort.[51,52] A single-day, 2-dose regimen demonstrated a 2-day reduction in median time to healing and overall efficacy equal to that of multiple day, lower-dose famciclovir regimens.[14] **Table 4** summarizes these data.

The efficacy of topical acyclovir cream used as treatment in primary or recurrent episodes of genital herpes varies between RCTs and overall does not appear to be as reliable as oral acyclovir.[56-58] Current Centers for Disease Control and Prevention guidelines discourage the use of the topical formulations, stating that they offer "minimal clinical benefit."[59]

CHRONIC SUPPRESSIVE THERAPY

Although most patients with HSV infections do not require CST, those with frequent recurrences who experience severe pain or disfigurement, have difficulty swallowing, or experience a protracted disease course are appropriately treated with CST.[8,9] Of all patients with labial herpes, 5% to 10% experience frequent recurrences (≥6 per year). Of patients infected with genital herpes, 20% to 50% have symptomatic, recurrent flares.[60] Patients have a median of 4 recurrences the year after a first symptomatic episode and usually enjoy a decline in frequency of outbreaks over time.[61,62] Recurrences of any frequency can negatively affect a patient's quality of life. Thus, CST is appropriate for patients who are psychologically distressed by their disease.[63] Long-term prophylactic therapy for genital herpes may also be used in an effort to decrease the risk of transmission to uninfected partners.[64,65]

CST in Recurrent Oral Herpes Simplex

Efficacy of acyclovir and valacyclovir as CST in patients with frequent recurrences of labial herpes has been demonstrated in RCTs. In the early 1990s, trials demonstrated that oral acyclovir (400 mg twice a day) was an effective mode of therapy. At the end of 4 months there was a 41% reduction in the number of patients experiencing labial herpes recurrences, and a 53% decrease in total number of outbreaks when compared with placebo-treated subjects.[8] The efficacy of valacyclovir was first demonstrated in a 4-month trial: valacyclovir prophylaxis (500 mg once a day) resulted in 60% of treatment group patients remaining disease free, compared with 38% of subjects in the placebo group. Mean time to first recurrence was significantly longer in the treatment group (13.1 weeks) compared with the control group (9.6 weeks).[9] In addition, a crossover study comparing valacyclovir given for 6 months as intermittent reactive therapy (two 2-g doses separated by 12 hours) and CST (1 g once daily) showed the chronic suppressive regimen to significantly decrease frequency of recurrences and pain severity scores.[66]

No RCTs have been conducted to specifically evaluate the ability of famciclovir to prevent recurrent labial herpes when given chronically (**Table 5**). The fact that short courses of prophylactic famciclovir (250 mg or 500 mg twice a day for 10 days started 1 day before the procedure) given in special circumstances (ie, facial laser resurfacing) have been shown to prevent recurrent episodes of labial herpes suggests long-term treatment may be efficacious.[67]

CST in Genital Herpes Simplex

Acyclovir was the first drug extensively studied and proven to markedly reduce genital herpes recurrences when taken daily for long periods in the immunocompetent population. A small trial in 1984 found that daily acyclovir (200 mg 3 times a day) taken for 125 days significantly decreased the number of genital herpes recurrences. All patients in the placebo group and 25% of subjects in the treatment group experienced at least 1 recurrence during a 4-month period.[68]

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Studies have focused on efficacy in suppressing recurrences, safety profile, optimal dosage, and the effect on recurrence rates after treatment is discontinued. During the first year of a 6-year multicenter trial, acyclovir (400 mg twice a day) significantly increased the number of patients remaining recurrence free (44% vs 2%) and median time to first outbreak (246 days vs 18 days) compared with placebo.[69] The following years of the trial demonstrated a "gradual and additional improvement" in response to therapy, with about 70% of patients remaining recurrence free during the fifth year of the trial.[62,69-71(p586)] Overall, studies suggest that acyclovir given as CST for 1 year allows 43% to 50% of patients to remain recurrence free, with a median time to first recurrence ranging from 246 to 274 days.[69,72-74] When control was not achieved at lower doses, most initial nonresponders were controlled with increased doses ranging from 1000 to 1600 mg/d.[62,75]

Unfortunately, once suppressive therapy is discontinued, outbreaks often recur. When discontinued within a year, episodes recur at a frequency comparable to subjects' baselines before chronic prophylactic therapy was initiated.[76] Of note, a prolonged treatment schedule of 5 years was shown in one study to lower recurrence rates relative to previous baseline in about two-thirds of patients.[70] To date, no RCTs have shown significant adverse effects related to prolonged treatment.[62,68-74,76-78]

The first RCT conducted on valacyclovir (500 mg once a day), a large 16-week study, demonstrated a significant reduction in recurrences (69% vs 9.5% recurrence free) and a significant increase in median time to first recurrence (>112 vs 20 days) in the treatment group compared with the placebo group.[79,80] Another study evaluating daily single-dose regimens (250 mg, 500 mg, and 1 g), 250 mg twice a day, 400 mg twice a day, and placebo found 500 mg once a day, 1 g once a day, 250 mg twice a day, and 400 mg twice a day of similar efficacy with regard to the percentage of patients remaining recurrence free (40%, 48%, 50%, and 49%, respectively) after 1 year. All these regimens were superior to the 250 mg once a day dosage (22% recurrence free) and placebo (5%).[80,81] More complete suppression was attained in patients with baseline disease activity of less than 10 recurrences per year, with the 500 mg once a day dosage typically sufficient for control. Patients with 10 or more recurrences per year often needed twice-daily dosing or 1 g once a day for adequate control.[80,81]

Famciclovir has also been proven effective as CST for genital herpes, demonstrating best efficacy when taken multiple times per days. A study conducted only in women evaluated multiple famciclovir dosages (125 mg once or twice daily, 250 mg once or twice daily, and 500 mg once a day) and found the famciclovir dosage of 250 mg twice a day to be the most effective regimen in significantly prolonging time to first clinically and virally confirmed recurrence. Once-daily dosing schedules were less effective or provided no significant benefit.[65] A larger study evaluating 250 mg of famciclovir twice a day demonstrated that 70% of those receiving the drug were recurrence free for 1 year, compared with only 20% of patients in the placebo group.[82] Various regimens of the drug (125 mg 3 times a day, 250 mg 3 times a day, and 250 mg twice a day) significantly increase time to first recurrence and percentage of patients remaining recurrence free for 1 year. Results attained with 250 mg of famciclovir twice a day or 3 times a day have been similar. Thus, the twice-daily dosing schedule has been suggested to provide a "convenient, effective, and well-tolerated regimen."[60(p892)]

The length of CST has not been defined by the Food and Drug Administration and is patient- and disease-course dependent.[70-72,78] Suppression for a year or longer is appropriate in many patients with frequent recurrences. Patients with herpes-associated erythema multiforme,[83] eczema herpeticum (Kaposi varicelliform eruption),[84] and herpetic keratitis,[85] and immunocompromised populations, including human immunodeficiency virus–positive individuals, may require indefinite suppressive therapy.[54,86-88] Acyclovir resistance occasionally occurs in immunocompromised patients.[88] A recent meta-analysis was performed to elucidate the best CST regimens for genital herpes (**Table 6**).[61]

Table 5. Chronic Suppressive Therapy for Labial Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved
Acyclovir	400 mg twice a day	II[8]	No
Valacyclovir hydrochloride	500 mg once a day	II[9]	No
	1 g once a day	II[66]	No
	500 mg twice a day[a]		
Famciclovir	500 mg twice a day	V[67]	No

Abbreviation: FDA, Food and Drug Administration.
[a]Human immunodeficiency virus–positive patients.

Table 6. Chronic Suppressive Therapy for Genital Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved	CDC Recommended
Acyclovir	400 mg twice a day	I[61,69,71,81]	Yes	Yes
	400-800 mg twice to 3 times a day[a]	I[89]	No	Yes
Valacyclovir hydrochloride	1 g once a day	I[81,90]	Yes	Yes
	500 mg once a day	I[79,80]	Yes	Yes
	500 mg twice a day[a]	I[89,91]	Yes	Yes
	250 mg twice a day	I[61,81]	No	No
Famciclovir	250 mg twice a day	I[60,65,82]	Yes	Yes
	500 mg twice a day[a]	II[87]	No	Yes

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.
[a]Human immunodeficiency virus–positive patients.

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Intermittent Suppressive Therapy

When recurrences can be anticipated, IST can be initiated to prevent oral and genital herpes outbreaks. Oral antiviral drugs are used for short periods when known precipitating factors might otherwise trigger reactivation of disease. Anticipatory treatment is also recommended in situations where decreasing viral shedding decreases the likelihood of infecting seronegative individuals with the virus.

Common stressors that can initiate herpes recurrences include ultraviolet radiation,[92-95] physical trauma or surgery,[5,7,96] emotional stress, menstrual cycles,[97-99] and hormonal factors. Clinical trials with topical (5% cream applied 5 times a day) and systemic (200 mg twice a day) acyclovir regimens have been proven effective in preventing sunlight-induced episodes of recurrent labial herpes.[92,94,95] Oral acyclovir and placebo groups experienced similar frequencies of labial herpes recurrences during the first few days of sun exposure. Significant reduction in number of recurrences became evident on the fifth day of treatment in the oral acyclovir group and during the 4-day follow-up period in the topical acyclovir group.[92,95] Prophylactic treatment has also been shown to significantly decrease recurrence rates of labial herpes in patients undergoing dental procedures. A study of patients prophylactically treated with valacyclovir before dental procedures found that clinical lesions appeared in 11.3% of test group patients and 20.6% of patients receiving a placebo, illustrating a 46% reduction in the number of clinically evident lesions.[7]

Intermittent suppressive therapy is also useful in special populations to decrease the risk of virus transmission to noninfected individuals. Although only 5% to 10% of reproductive-age women have a history of genital herpes lesions, 25% to 30% are seropositive for HSV type 2. Roughly 5% to 10% of pregnant women experience a symptomatic herpes infection at some point during pregnancy. If such a recurrence occurs during the peripartum period, especially if the infection is primary, consequences to the fetus can be devastating. These cases are routinely managed with cesarean section, but anticipatory treatment offers a more practical solution. Decision making can be guided with vaginal herpes cultures at regular intervals during the third trimester. Acyclovir initiated at 36 weeks' gestation has significantly reduced the rate of HSV recurrence in several small studies.[100-102] Trials have also proven valacyclovir effective in significantly decreasing clinical recurrences and asymptomatic viral shedding.[103,104]

Intermittent suppressive therapy can also prevent viral transmission to uninfected athletes competing in wrestling (herpes gladiatorum) and rugby.[105] A 2003 study of prophylactic valacyclovir was conducted at a month-long wrestling camp. Two diagnostically confirmed outbreaks were reported compared with 15 to 20 outbreaks in 2002 and 57 outbreaks in 2001, conferring 78% and 87% decreases in outbreaks, respectively.[106]

Dosing recommendations for IST of oral and genital herpes infections have not been published, but it has been our experience that using the same dosing during periods when outbreaks are anticipated as those used in long-term suppressive therapy is quite effective (Table 5 and Table 6).

Accepted for Publication: December 18, 2007.

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Author Contributions: Drs Cernik and Brodell had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Gallina and Brodell. *Acquisition of data:* Cernik. *Analysis and interpretation of data:* Cernik and Brodell. *Drafting of the manuscript:* Cernik and Brodell. *Critical revision of the manuscript for important intellectual content:* Gallina and Brodell. *Study supervision:* Gallina and Brodell.

Financial Disclosure: Dr Brodell has received honoraria for speaking engagements from Novartis (manufacturer of Famvir) and GlaxoSmithKline (manufacturer of Valtrex and Zovirax).

REFERENCES

1. Klein RS. Epidemiology of herpes simplex virus type 1 infection. http://uptodate.com/. Accessed February 1, 2008.
2. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. 2006; 296(8):964-973.
3. Arduino PG, Porter SR. Oral and perioral herpes simplex virus type 1 (HSV-1) infection: review of its management. *Oral Dis*. 2006;12 (3):254-270.
4. Kolokotronis A, Doumas S. Herpes simplex virus infection, with particular reference to the progression and complications of primary herpetic gingivostomatitis. *Clin Microbiol Infect*. 2006; 12(3):202-211.
5. Bisaccia E, Scarborough D. Herpes simplex virus prophylaxis with famciclovir in patients undergoing aesthetic facial CO_2 laser resurfacing. *Cutis*. 2003;72(4):327-328.
6. Nikkels AF, Pièrard GE. Treatment of mucocutaneous presentations of herpes simplex virus infections. *Am J Clin Dermatol*. 2002;3(7): 475-487.
7. Miller CS, Cunningham LL, Lindroth JE, Avdiushko SA. The efficacy of valacyclovir in preventing recurrent herpes simplex virus infections associated with dental procedures. *J Am Dent Assoc*. 2004;135(9):1311-1318.
8. 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(4):268-272.
9. Baker D, Eisen D. Valacyclovir for prevention of recurrent herpes labialis: 2 double-blind, placebo-controlled studies. *Cutis*. 2003;71 (3):239-242.
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(1):47-53.
11. Woo S, Challacombe SJ. Management of recurrent oral herpes simplex infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007; 103(suppl):S12.e1-S12.e18.
12. Felman YM, Nikitas JA. Genital herpesvirus infection. *N Y State J Med*. 1979;79(8):1216-1218.
13. Engel JP. Long-term suppression of genital herpes. *JAMA*. 1998;280(10):928-929.
14. Aoki FY, Tyring S, Diaz-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(1):8-13.
15. Solomon L, Cannon MJ, Reyes M, Graber JM, Wetherall NT, Reeves WC; Task Force on Herpes Simplex Virus Resistance. Epidemiology of recurrent genital herpes simplex virus types 1 and 2. *Sex Transm Infect*. 2003;79(6): 456-459.
16. 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(2):89-94.

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17. Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med*. 1999;131(1):14-20.
18. Rosen T. Sexually transmitted diseases 2006: a dermatologist's view. *Cleve Clin J Med*. 2006; 73(6):537-538, 542, 544-545.
19. Mindel A. Genital herpes: the forgotten epidemic. *J Herpes*. 1994;1(2):39-48.
20. Beauman JG. Genital herpes: a review. *Am Fam Physician*. 2005;72(8):1527-1534.
21. 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 (7097):1800-1803.
22. Chauvin PJ, Ajar AH. Acute herpetic gingivostomatitis in adults: a review of 13 cases, including diagnosis and management. *J Can Dent Assoc*. 2002;68(4):247-251.
23. Spruance SL, Stewart JC, Rowe NH, McKeough MB, Wenerstrom G, Freeman DJ. Treatment of recurrent herpes simplex labialis with oral acyclovir. *J Infect Dis*. 1990;161(2):185-190.
24. Spruance S, Jones T, Blatter M, 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(3):1072-1080.
25. Chacko M, Weinberg J. Famciclovir for cutaneous herpesvirus infections: an update and review of new single-day dosing indications. *Cutis*. 2007;80(1):77-81.
26. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T; Acyclovir Cream Study Group. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother*. 2002; 46(7):2238-2243.
27. Chon T, Nguyen L, Elliott TC. Clinical inquiries: what are the best treatments for herpes labialis? *J Fam Pract*. 2007;56(7):576-578.
28. Raborn GW, Martel AY, Lassonde M, Lewis MA, Boon R, Spruance SL. Effective treatment of herpes simplex with penciclovir cream: combined results of two trials. *J Am Dent Assoc*. 2002; 133(3):303-309.
29. Fiddian AP, Yeo JM, Stubbings R, Dean D. Successful treatment of herpes labialis with topical acyclovir. *Br Med J (Clin Res Ed)*. 1983; 286(6379):1699-1701.
30. Van Vloten WA, Swart RN, Pot F. Topical acyclovir therapy in patients with recurrent orofacial herpes simplex infections. *J Antimicrob Chemother*. 1983;12(suppl B):89-93.
31. Femiano F, Gombos F, Scully C. Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared with acyclovir. *Oral Dis*. 2001; 7(1):31-33.
32. Spruance SL, Rea TL, Thoming C, Tucker R, Saltzman R, Boon R. Penciclovir cream for the treatment of herpes simplex labialis: a randomized, multicenter, double-blind, placebo-controlled trial. *JAMA*. 1997;277(17):1374-1379.
33. Raborn GW, McGaw WT, Grace M, Houle L. Herpes labialis treatment with acyclovir 5 per cent ointment. *J Can Dent Assoc*. 1989;55 (2):135-137.
34. Raborn GW, McGaw WT, Grace M, Percy J, Samuels S. Herpes labialis treatment with the acyclovir 5% modified aqueous cream: a double-blind randomized trial. *Oral Surg Oral Med Oral Pathol*. 1989;67(6):676-679.
35. Spruance SL, Rowe NH, Raborn GW, Thibodeau EA, D'Ambrosio JA, Bernstein DI. 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(2): 303-310.
36. Boon R, Goodman JJ, Martinez J, Marks GL, Gamble M, Welch C. Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. *Clin Ther*. 2000;22 (1):76-90.
37. Lin L, Chen XS, Cui PG, et al. Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicenter, acyclovir-controlled trial. *J Dermatolog Treat*. 2002;13(2):67-72.
38. Mertz GJ, Critchlow CW, Benedetti J, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. *JAMA*. 1984;252(9):1147-1151.
39. Wald A, Benedetti J, Davis G, Remington M, Winter C, Corey L. A randomized, double-blind, comparative trial comparing high- and standard-dose oral acyclovir for first-episode genital herpes infections. *Antimicrob Agents Chemother*. 1994; 38(2):174-176.
40. Fife KH, Barbarash RA, Rudolph T, Degregorio B, Roth R; Valaciclovir International Herpes Simplex Virus Study Group. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection: results of an international, multicenter, double-blind, randomized clinical trial. *Sex Transm Dis*. 1997;24(8):481-486.
41. Fiddian AP, Halsos AM, Kinge BR, Nilsen AE, Wikstrom K. Oral acyclovir in the treatment of genital herpes preliminary report of a multicenter trial. *Am J Med*. 1982;73(1A):335-337.
42. Loveless M, Sacks SL, Harris JR. Famciclovir in the management of first-episode genital herpes. *Infect Dis Clin Pract*. 1997;6(1)(suppl):S12-S16.
43. Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs*. 2006;66(18): 2397-2416.
44. Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. *JAMA*. 1984;251(16):2103-2107.
45. Bodsworth NJ, Crooks RJ, Borelli S, et al. Valacyclovir versus acyclovir in patient initiated treatment of recurrent genital herpes: a randomised, double blind clinical trial. *Genitourin Med*. 1997;73(2):110-116.
46. Goldberg LH, Kaufman R, Conant MA, et al. Oral acyclovir for episodic treatment of recurrent genital herpes. *J Am Acad Dermatol*. 1986; 15(2, pt 1):256-264.
47. Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis*. 2002;34(7): 944-948.
48. Saiag P, Praindhui D, Chastang C. A double-blind, randomized study assessing the equivalence of valacyclovir 1000 mg once daily versus 500 mg twice daily in the episodic treatment of recurrent genital herpes. *J Antimicrob Chemother*. 1999;44(4):525-531.
49. Leone PA, Trottier S, Miller JM. Valacyclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. *Clin Infect Dis*. 2002;34(7): 958-962.
50. Spruance SL, Tyring SK, DeGregorio B, Miller C, Beutner K; Valaciclovir HSV Study Group. A large-scale, placebo-controlled, dose-ranging trial of peroral valacyclovir for episodic treatment of recurrent herpes genitalis. *Arch Intern Med*. 1996;156(15):1729-1735.
51. Sacks SL, Aoki FY, Siaz-Mitoma F, Sellors J, Shafran SD; Canadian Famciclovir Study Group. Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes: a randomized, double-blind multicenter trial. *JAMA*. 1996; 276(1):44-49.
52. Sacks SL, Aoki FY, Martel AY, Shafran SD, Lassonde M. Clinic-initiated, twice-daily oral famciclovir for treatment of recurrent genital herpes: a randomized, double-blind, controlled trial. *Clin Infect Dis*. 2005;41(8):1097-1104.
53. Tyring SK, Douglas JM, Corey L, Spruance SL, Esmann J; Valaciclovir International Study Group. A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. *Arch Dermatol*. 1998;134(2): 185-191.
54. Warren T, Harris J, Brennan CA. Efficacy and safety of valacyclovir for the suppression and episodic treatment of herpes simplex virus in patients with HIV. *Clin Infect Dis*. 2004;39(suppl 5):S258-S266.
55. Romanowski B, Aoki FY, Martel AY, Lavender EA, Parsons JE, Saltzman RL. Efficacy and safety of famciclovir for treating mucocutaneous herpes simplex infection in HIV-infected individuals. *AIDS*. 2000;14(9):1211-1217.
56. Chen XS, Han GZ, Guo ZP, Lu NZ, Chen J, Wang JB. A comparison of topical application of penciclovir 1% cream with acyclovir 3% cream for treatment of genital herpes: a randomized, double-blind, multicenter trial. *Int J STD AIDS*. 2000;11(9):568-573.
57. Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW, Holmes KK. A trial of topical acyclovir in genital herpes simplex virus infections. *N Engl J Med*. 1982;306(22):1313-1319.
58. Corey L, Benedetti J, Critchlow C, et al. Treatment of primary first-episode genital herpes simplex virus infections with acyclovir: results of topical, intravenous, and oral therapy. *J Antimicrob Chemother*. 1983;12(suppl B):79-88.
59. Centers for Disease Control and Prevention, Division of STD Prevention. Sexually transmitted diseases: treatment guidelines 2006. http://www.cdc.gov/std/treatment/2006/genital-ulcers.htm#genulc3. Accessed March 7, 2008.
60. Diaz-Mitoma F, Sibbald RG, Shafran SD, Boon R, Saltzman RL. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. *JAMA*. 1998;280(10): 887-892.
61. Lebrun-Vignes B, Bouzamondo A, Dupuy A, Guillaume JC, Lechat P, Chosidow O. A meta-analysis to assess the efficacy of oral antiviral treatment to prevent genital herpes outbreaks. *J Am Acad Dermatol*. 2007;57(2): 238-246.
62. Kaplowitz LG, Baker D, Gelb L, et al. Prolonged continuous acyclovir treatment of normal adults with frequently recurring genital herpes simplex virus infection. *JAMA*. 1991;265(6): 747-751.
63. Brentjens MH, Yeung-Yue KA, Lee PC, Tyring SK. Recurrent genital herpes treatments and their impact on quality of life. *Pharmacoeconomics*. 2003;21(12):853-863.
64. Corey L, Wald A, Patel R, et al. Once-daily valacy-

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clovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. 2004;350(1):11-20.
65. Mertz GJ, Loveless MO, Levin MJ, et al. Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women: a multicenter, double-blind, placebo-controlled trial. *Arch Intern Med*. 1997;157(3):343-349.
66. 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(4):400-405.
67. Alster TS, Nanni CA. Famciclovir prophylaxis of herpes simplex virus reactivation after skin resurfacing. *Dermatol Surg*. 1999;25(3):242-246.
68. Straus SE, Takiff HE, Seidlin M, et al. Suppression of frequently recurring genital herpes: a placebo-controlled, double-blind trial of oral acyclovir. *N Engl J Med*. 1984;310(24):1545-1550.
69. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex infection: a multicenter double-blind trial. *JAMA*. 1988;260(2):201-206.
70. Fife KH, Crumpacker CS, Mertz GJ, Hill EL, Boone GS; Acyclovir Study Group. Recurrence and resistance patterns of herpes simplex virus following cessation of ≥6 years of chronic suppression with acyclovir. *J Infect Dis*. 1994;169(6):1338-1341.
71. Goldberg LH, Kaufman R, Kurtz TO, et al. Long-term suppression of recurrent genital herpes with acyclovir: a 5-year benchmark. *Arch Dermatol*. 1993;129(5):582-587.
72. Mostow SR, Mayfield JL, Marr JJ, Drucker JL. Suppression of recurrent genital herpes by single daily dosages of acyclovir. *Am J Med*. 1988;85(2A):30-33.
73. Mattison HR, Reichman RC, Benedetti J, et al. Double-blind, placebo-controlled trial comparing long-term suppressive with short-term oral acyclovir therapy for management of recurrent genital herpes. *Am J Med*. 1988;85(2A):20-25.
74. Baker DA, Blythe JG, Kaufman R, Hale R, Portnoy J. One-year suppression of frequent recurrences of genital herpes with oral acyclovir. *Obstet Gynecol*. 1989;73(1):84-87.
75. Straus SE, Croen KD, Sawyer MH, et al. Acyclovir suppression of frequently recurring genital herpes: efficacy and diminishing need during successive years of treatment. *JAMA*. 1988;260(15):2227-2230.
76. Sacks SL, Fox R, Levendusky P, et al. Chronic suppression for six months compared with intermittent lesional therapy of recurrent genital herpes using oral acyclovir: effects on lesions and nonlesional prodromes. *Sex Transm Dis*. 1988;15(1):58-62.
77. Douglas JM, Critchlow C, Benedetti J, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. *N Engl J Med*. 1984;310(24):1551-1556.
78. Mindel A, Weller IV, Faherty A, et al. Prophylactic oral acyclovir in recurrent genital herpes. *Lancet*. 1984;2(8394):57-59.
79. Patel R, Bodsworth NJ, Woolley P, et al; International Valacyclovir HSV Study Group. Valacyclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once daily therapy. *Genitourin Med*. 1997;73(2):105-109.
80. Ormrod D, Scott LJ, Perry CM. Valacyclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs*. 2000;59(4):839-863.
81. Reitano M, Tyring S, Lang W, 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(3):603-610.
82. Tyring SK, Diaz-Mitoma F, Shafran SD, Locke LA, Sacks SL, Young CL. Oral famciclovir for the suppression of recurrent genital herpes: the combined data from two randomized controlled trials. *J Cutan Med Surg*. 2003;7(6):449-454.
83. Kerob D, Assier-Bonnet H, Esnault-Gelly P, Blanc F, Saiag P. Recurrent erythema multiforme unresponsive to acyclovir prophylaxis and responsive to valacyclovir continuous therapy. *Arch Dermatol*. 1998;134(7):876-877.
84. Olson J, Robles DT, Kirby P, Colven R. Kaposi varicelliform eruption (eczema herpeticum). *Dermatol Online J*. 2008;14(2):18. http://dermatology.cdlib.org/142/case_presentations/eczemaherp/olson.html/. Accessed April 7, 2008.
85. Herpetic Eye Disease Study Group. Oral acyclovir for herpes simplex virus eye disease: effect on prevention of epithelial keratitis and stromal keratitis. *Arch Ophthalmol*. 2000;118(8):1030-1036.
86. McNeeley DF, Polsky B. Prophylaxis of viral infections in patients with cancer. *Infect Med*. 1995;12(5):203-204, 207-210.
87. Schacker T, Hu HL, Koelle DM, et al. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons: a double-blind, placebo-controlled trial. *Ann Intern Med*. 1998;128(1):21-28.
88. Chilukuri S, Rosen T. Management of acyclovir-resistant herpes simplex virus. *Dermatol Clin*. 2003;21(2):311-320.
89. Conant MA, Schacker TW, Murphy RL, Gold J, Crutchfield LT, Crooks RJ. Valacyclovir versus acyclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. *Int J STD AIDS*. 2002;13(1):12-21.
90. Fife KH, Warren TJ, Ferrera RD, 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(10):1321-1327.
91. DeJesus E, Wald A, Warren T, et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. *J Infect Dis*. 2003;188(7):1009-1016.
92. Spruance SL, Hamill ML, Hoge WS, Davis LG, Mills J. Acyclovir prevents reactivation of herpes simplex labialis in skiers. *JAMA*. 1988;260(11):1597-1599.
93. Rooney JF, Straus SE, Mannix ML, et al. UV light–induced reactivation of herpes simplex virus type 2 and prevention by acyclovir. *J Infect Dis*. 1992;166(3):500-506.
94. Nelson MA. Stopping the spread of herpes simplex: a focus on wrestlers. *Phys Sportsmed*. 1992;20(10):117-127.
95. Raborn GW, Martel AY, Grace MGA, McGaw WT. Herpes labialis in skiers: randomized clinical trial of acyclovir cream versus placebo. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;84:641-645.
96. Beeson WH, Rachel JD. Valacyclovir prophylaxis for herpes simplex virus infection or infection recurrence following laser skin resurfacing. *Dermatol Surg*. 2002;28(4):331-336.
97. Guinan ME, MacCalman J, Kern ER, Overall JC, Spruance SL. The course of untreated recurrent genital herpes simplex infection in 27 women. *N Engl J Med*. 1981;304(13):759-763.
98. Segal AL, Katcher AH, Brightman VJ, Miller MF. Recurrent herpes labialis, recurrent aphthous ulcers, and the menstrual cycle. *J Dent Res*. 1974;53(4):797-803.
99. Myśliwska J, Trzonkowski P, Bryl E, Lukaszuk K, Myesliwski A. Lower interleukin-2 and higher serum tumor necrosis factor-a levels are associated with perimenstrual, recurrent, facial herpes simplex infection in young women. *Eur Cytokine Netw*. 2000;11(3):397-406.
100. Prober CG. Reducing the risk of perinatal transmission of herpes simplex virus type 2. *Infect Med*. 1993;10(3):21-24, 27-28, 44.
101. 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(6):1396-1403.
102. Scott LL, Hollier LM, McIntire D, Sanchez PJ, Jackson GL, Wendel GD. Acyclovir suppression to prevent clinical recurrences at delivery after first episode genital herpes in pregnancy: an open-label trial. *Infect Dis Obstet Gynecol*. 2001;9(2):75-80.
103. Sheffield JS, Hill JB, Hollier LM, et al. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. *Obstet Gynecol*. 2006;108(1):141-147.
104. 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(3):774-781.
105. Rosenbaum GS, Strampfer MJ, Cunha BA. Herpes gladiatorum in a male wrestler. *Int J Dermatol*. 1990;29(2):141-142.
106. Anderson BJ. Prophylactic valacyclovir to prevent outbreaks of primary herpes gladiatorum at a 28-day wrestling camp. *Jpn J Infect Dis*. 2006;59(1):6-9.

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