

# Genital herpes: diagnosis and treatment

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**ABSTRACT** Sexually transmitted infections, including genital herpes, are on the increase. One in every five Americans is now known to be HSV-2 seropositive, yet subclinical infection and asymptomatic patients result in under diagnosis of this common condition. Data show that most patients are unaware of their infection and may, therefore, unknowingly spread the virus to others: silent spread of HSV is the rule, not the exception. Teens and women are at highest risk for infection. Patient education regarding condom use and abstinence, combined with early recognition and treatment, are the most effective ways to halt this pandemic.

Two types of herpes simplex viruses (HSV) are capable of causing genital disease: HSV-1 and HSV-2. Although these types tend to produce subtly different clinical presentations, they result in the same clinical picture.

HSV-1 most commonly causes oral lesions—euphemistically referred to as cold sores, sun blisters, or fever blisters—on the lips (Figure 1) and nostrils. Most patients do not realize that these lesions are caused by the herpes virus, and are unaware of the potential infectious implications. HSV-1 seropositivity is very common, affecting 60% to 85% of the US population,<sup>1</sup> and most of these infections are acquired during childhood by oral contact.

Although HSV-1 is the virus responsible for nearly all oro-labial herpes some cases may result from HSV-2.<sup>2</sup> In contrast, HSV-2 is responsible for most genital lesions.<sup>3</sup> Therefore, although HSV-1 accounts for the majority of infections above the waist, and HSV-2 accounts for those below the waist, either viral type can cause lesions in both locations. Transmission of either type can be caused by oral-oral, oral-genital, or genital-genital contact.

## Risk factors

**Age.** A recent study has shown that more than one in five Americans over the age of 12 are infected with the HSV-2 virus, and one million new cases occur annually.<sup>4</sup> Those at greatest risk for genital herpes infection are people under the age of 30 and those with multiple sex partners. However, anyone who has close sexual contact with an infected person, even once, is at risk for the disease.<sup>4</sup> One of the fastest growing segments of the population to acquire genital herpes is teens, who were recently found to be five times more likely to be HSV-2 seropositive compared with figures from 1976 and 1980.<sup>4</sup>

## Practice Tips

- | Be sure to inform your HSV-infected patients that they are still potentially infectious, even between attacks.
- | Remind patients to maintain condom use during suppressive therapy.
- | While taking cultures, remember to swab firmly and vigorously to attain the virus, which is located intracellularly.
- | Episodic treatment of recurrent attacks needs to be initiated within 24 hours of lesion onset in order to be maximally effective.

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Dr Baldwin is on the Speaker's  
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**FIGURE 1**  
**Oro-labial herpes**

Primary herpes infection of the lips and surrounding skin caused by HSV-1.



**FIGURE 2**  
**Genital herpes infection in the vulva**



**FIGURE 3**  
**Herpetic whitlow-HSV infection**

Herpetic whitlow-HSV infection of the finger may occur from transmission of primary oral or genital herpes by inoculation of virus through a break in the skin.

**Gender.** Gender is also a factor in risk of infection; women are 45% more likely to be infected with HSV-2 than are men,<sup>4</sup> and transmission is more efficient from men to women.<sup>5</sup>

**Concurrent infections.** Because of the damage done to the mucous membranes by open, raw herpes lesions, acquisition of other infections such as syphilis, gonorrhea, or HIV are more probable in HSV-infected patients. In addition, patients who have both HIV and HSV infections are far more likely to transmit both diseases to their sexual partners.<sup>6</sup> In HIV-infected patients with herpes lesions, a swab of the ulcer base reveals both HSV and HIV virus. Therefore, genital herpes lesions represent a danger to both the patient and his/her potential sexual partners. There is also evidence that HSV acquisition may accelerate HIV immunosuppression.

### Clinical findings

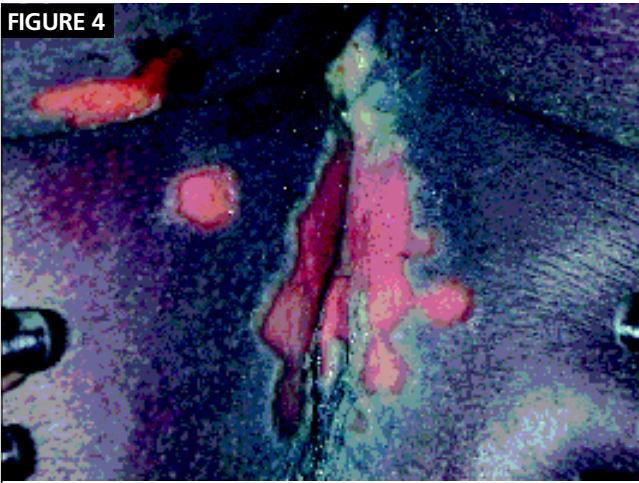
**Primary infection.** Herpes infections become easily established once the virus has been introduced through a mucous membrane. The establishment of infection may be accomplished more readily at an abraded surface, which may be the result of more mechanically abrasive sex (eg, under-lubricated sex, anal sex). The incubation period is 7 to 21 days, and 95% of patients presenting with primary disease have acquired the infection within the past 2 weeks. The primary attack of genital HSV is usually the most severe and the longest lasting with grouped vesicles, sometimes in multiple crops, on an

erythematous base occurring anywhere in the genital area (Figure 2). The ulcerations are generally painful, and may be accompanied by local lymphadenopathy and low-grade fever. Patients with severe infections can develop the inability to void or defecate. Most patients with primary attacks experience lesions and/or pain for 10 to 14 days. Infection with HSV can cause lesions anywhere on the body. Herpetic whitlow of the finger can be caused by infected human bites and is seen most often in dentists (Figure 3).

After the initial attack has subsided, the virus travels up the corresponding spinal nerve to the spinal ganglion, where it becomes latent for an unknown period of time. The virus does not multiply during latency, and is protected from both the host's immune system and from pharmaceutical agents by virtue of its hiding place within the avascular ganglion.

**Recurrent attacks.** Recurrent attacks are prompted by various common circumstances or may occur without any evident provocation. Common causes include concomitant medical and surgical conditions, stressful situations, and menses. Once the recurrent attack begins, the virus rapidly multiplies and begins its trip back down the nerve to the skin where blisters form. Recurrent events are milder and shorter-lived than the initial attack. Again, the patient presents with tender, grouped

FIGURE 4



**HSV-2 infection on buttock**

Multiple perianal eruptions of HSV-2 in a female patient with HIV. This patient was resistant to acyclovir treatment.

Courtesy of Mary Gail Mercurito, MD, Rochester, NY

FIGURE 5



**Erythema multiforme**

This disease should alert you to the presence of HSV infection.

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vesicles on an erythematous base. A single crop of vesicles is the rule, and lymphadenopathy, fever, and associated systemic symptoms are rare. Most patients are lesion- and pain-free at 7 to 10 days.

Recurrent attacks occur most frequently within the first year of viral acquisition, and become less frequent with advancing years.<sup>7</sup> Lesions generally occur within the genital area, but due to the complexity of the sacral plexus, genitally acquired infections can recur on the buttock, lower back, and upper thigh posteriorly. One study showed that 21% of genital herpes patients will experience an extragenital recurrence.<sup>8</sup> For patients with HSV-2, these recurrences were characteristically on the buttock (Figure 4). Because of the location, these lesions are commonly misdiagnosed by clinicians, and patients are surprised when they are eventually diagnosed with HSV, although the morphology of the lesions are identical to those of herpes outbreaks elsewhere.

**Cutaneous sequelae of HSV infection**

Two cutaneous diseases can occur in response to HSV infections: erythema multiforme and eczema herpeticum (Kaposi's varicelliform eruption).

**Erythema multiforme.** Erythema multiforme (Figure 5) is a reaction pattern of the skin that occurs in response to infection exclusively with HSV. Erythema multiforme

presents as pink-red and white target lesions and targetoid papules in a primarily acral distribution, which occur within several days of the onset of a herpes outbreak. Severe erythema multiforme may cause widespread lesions that can blister and ulcerate. In

erythema multiforme major (Stevens-Johnson syndrome), mucous membranes, most commonly the lips, are involved in 10% of cases.<sup>9</sup> In these locations, it causes erosive plaques that can limit eating and drinking, leading to dehydration and, in some cases, death. Anal and urethral lesions can prevent evacuation. These lesions will occur

with regularity with each herpes outbreak, and can be far more severe than the herpes eruption itself.

**Eczema herpeticum.** Eczema herpeticum (Figure 6) is a herpes outbreak that spreads cutaneously rather than systemically. No viremia occurs; rather the virus spreads widely to involve small tears and cuts in skin previously injured by eczema or a similar eruption. It occurs most commonly in children and young adults, the population most highly affected by eczema. Patients are covered with small vesicles throughout the eczematous patches, and secondary infection and scarring are common. This condition may also recur with each herpes outbreak.

**Subclinical shedding and asymptomatic disease**  
**Subclinical infection.** Of the 50 million Americans who have genital herpes, only a fraction recognize this fact.<sup>10</sup>

**Women are more likely to be infected with HSV-2 than men, and transmission is more effective from men to women.**



**FIGURE 6**

**Eczema herpeticum**

A potential sequela to genital HSV infection, this condition is most common in children and young adults.

In the NHANES study, only 10% of those patients who were seropositive reported ever having had signs of genital herpes.<sup>4</sup> A recent study shows that nearly 40% of new HSV-2 and 75% of HSV-1 infections are asymptomatic.<sup>11</sup> This is partially because some patients have subclinical infections; however, recent studies have shown that 50% to 87% of patients who denied ever having had genital herpes lesions recognized symptoms of herpes once adequately counseled during the study period.<sup>12,13</sup> Education of the public, therefore, could go a long way in improving herpes diagnosis and prevention. Some patients, however, clearly have subclinical disease without clinical evidence of lesions. These patients shed virus regularly and are at high risk for infecting their sexual partners.

**Asymptomatic patients.** Be sure to inform your HSV-infected patients that they are still potentially infectious between attacks; this has been shown by daily genital swabs combined with lesion and symptom diaries.<sup>14,15</sup> Seropositive patients without clinical lesions show periods of shedding lasting several days, simulating an active attack.<sup>14,16</sup> During a clinical attack, virus is shed in higher concentrations. Shedding is even higher in HIV-infected women.<sup>17</sup> Therefore, male pa-

tients with herpes, or trying to avoid herpes, must always wear condoms when engaged in genital contact, both during, as well as between, attacks. But even this precaution is not fully reliable because the site of shedding may not be localized to the limited penile surface covered by the condom.

For several reasons, it is likely that most new acquisitions of genital herpes occur during periods of lesion inactivity. First, genital herpes is sufficiently painful so that most patients do not engage in intercourse during an active attack. Second, since attacks last for up to 7 to 10 days, and the intervening periods are longer, there is more time to acquire disease during periods without evident lesions. Finally, when lesions are not evident, condom use may be less vigilant. Although studies have shown that antiviral agents decrease subclinical shedding,<sup>13</sup> there are concerns that complete drug suppression of clinically evident disease will further reduce condom use.

**Prevention**

The combination of condom use, antiviral medications, and abstinence during active outbreaks are the best ways to help prevent transmission. Since all of these issues hinge on adequate patient education, our job as physicians is to discuss sexual issues with all patients; taking the time to educate our teen patients is particularly important.

**Diagnostic procedures**

**Western blot.** Diagnostic techniques include viral culture, serologic tests, and Western blot analysis. Viral culture taken from active vesicular lesions is the easiest, fastest, and cheapest method for diagnosis. While taking cultures, remember to swab firmly and vigorously to attain the virus, which is located intracellularly. However, frequently a patient will present with a history of a genital lesion that is no longer present or has crusted over, rendering it noninfectious. In these cases, cultures can detect recurrent disease about 50% of the time. Cytology cannot distinguish between HSV-1, HSV-2, and herpes zoster. Serologic tests for HSV-1 and HSV-2 exist, but are often not helpful. Crossover between the viruses can make it difficult to tell which viral type is responsible for the positive serologic test.<sup>14</sup> Because HSV-1 is so common, a positive test usually does not help. However, type specific serologies will soon be available at specialized laboratories. Also, since both type 1 and type 2 can cause genital lesions, and because the titer stays positive for life, a blood test indicating type 1

positivity could indicate last month's cold sore or today's genital ulcer. This can result in titers that are inappropriately interpreted to suggest infidelity in one partner. If the affected partner is HSV positive and the other is HSV negative, infection necessarily occurred from outside the relationship. However, this need not have been any time in the recent past, since a positive test does not help us to determine the timeframe of the infection. A first clinically apparent outbreak may represent disease that has been latent for an extended period of time.

Western blot analysis is the most sensitive and specific test for either type herpes virus. Unfortunately, it is also the most expensive. Since the vast majority of genital herpes attacks can be diagnosed either by clinical appearance or culture, the cost is often hard to justify. There is one clinical scenario in which I frequently utilize Western blot analysis: a monogamous herpes-discordant couple presenting for the purpose of identifying ways in which to avoid contagion while permitting the possibility of pregnancy. This couple needs the most sophisticated detection method at our disposal to generate a valid conclusion. Considering the high prevalence of HSV-2 in the US population, it is possible that the "negative" partner is actually HSV-2 positive. Uncovering this information would free the couple from a lifetime of trying to prevent infection in someone who is already infected. A Western blot may become positive as early as 2 weeks after initial infection, but is more reliably done 12 weeks later. A negative test at first presentation, coupled with a positive test at week 12, confirms that the attack is the initial, primary attack.

**POCkit.** The POCkit® HSV-2 Rapid Test was recently approved by the FDA and is intended for use in the office setting. This test identifies HSV-2 only, is 90% to 95% sensitive, and is much less expensive than the Western blot. The inability of the test to detect HSV-1, and its reduced sensitivity compared to the Western blot, limits its use.<sup>18</sup> Difficulty with physician reimbursement for this test is another issue to consider. Availability of the POCkit test in the US is currently limited to specialized facilities in 26 states. More information is available on [www.pockit.com](http://www.pockit.com).

### Treatment considerations

Herpes simplex treatment is limited because of the peculiarities of the virus, and the outcome is limited to shortening the current attack and preventing recurrence. We still do not have any pharmacologic method for eradicating viruses of any sort from the human body.

Generally, the immune system overwhelms the virus, and ultimately destroys it, rendering the patient immune for life. However, herpes viruses are uniquely able to isolate themselves within neural tissue. Neural tissue is relatively avascular, and so the herpes virus living within it is impervious to attack by both bloodborne pharmaceutical agents and the immune system.

The herpes virus also spends a long part of its life in a dormant, latent phase. Since antiviral agents become activated by viral replication enzymes, they are active only when the virus is replicating in preparation for a recurrent attack. Even then, the agents can only reach the virus once it arrives at the skin surface—the virus travels down the sensory nerve to the surface of the skin where lesions then form—and presents itself to the bloodstream and the immune system. Together, the immune system and medications are able to reduce lesion number, pain, and duration. Clinical suppression of attacks is also possible via the same mechanism, although the treated patient likely sheds asymptotically, as the medications should only be capable of attacking the virus once it has reached the skin surface.

**Drug therapy.** Several agents are useful for the treatment of genital herpes. Acyclovir, famciclovir, and valacyclovir (Table) are most commonly used due to their oral efficacy and good safety record. All three agents are acted upon by viral thymidine kinase, an enzyme necessary for viral replication. As such, in the rare occurrence of viral drug resistance, replacement with another drug in this category would not be expected to improve the clinical response.

Acyclovir has been the benchmark drug for many years, but has several drawbacks that were tolerated because of its superb safety record. These drawbacks have included poor oral absorption that necessitated a five times a day dosing schedule, and limits compliance. Absorption of acyclovir is also inhibited by gastric contents, a problem that is magnified by a five-time per day dosing schedule.

The two newer agents, valacyclovir and famciclovir, have an easier once or twice daily dosing schedule which is significant in patients who are already on multiple medications. Once they gain access to the infected cells, acyclovir and valacyclovir have an intracellular half-life of 1 to 2 hours. Famciclovir has a much longer intracellular half-life of 10 to 20 hours, but consequent increase in efficacy has not been seen clinically. All three medications have a 2 to 3 hour plasma half-life and are excreted renally.

**Treating primary attacks.** Drug therapy of primary attacks is often hindered by the delay in seeking treat-

**TABLE Antiviral drug therapy for genital herpes**

Drug	Dose primary attack	Dose recurrent attack	Dose suppressive therapy	Oral absorption
Acyclovir (Zovirax®)	200 mg 5x/day 400 mg 3x/day x 7 days	200 mg 5x/day 400 mg 3x/day 800 mg 2x/day x 5 days	400 mg 2x/day 200 mg 5x/day	10–20%
Famciclovir (Famir®)	250 mg 2x/day x 7 days	125 mg 2x/day x 5 days	250 mg 2x/day	77%
Valacyclovir (Valtrex®)	1000 mg/day x 7 days	500 mg 2x/day x 5 days	500-1000 mg/day	54%

NOTE: Reported side effects of these medications, which are rare, are comparable to placebo in most cases.

ment. By the time the lesions are clinically evident, the condition is progressing rapidly. Because primary attacks are more severe than recurrent attacks, higher doses or more frequent dosing may be necessary.

Studies on mice showed that the use of famciclovir in primary attacks can eradicate the virus and prevent the establishment of latency.<sup>19</sup> Although not yet shown in humans, this is an intriguing possibility worth remembering in patients presenting with primary disease or exposure to a known HSV-positive partner.

**Treating recurrent events.** Episodic treatment of recurrent attacks needs to be initiated within 24 hours of lesion onset in order to be maximally effective.<sup>20</sup> Therapy initiated beyond 72 hours has a limited chance of being effective unless a second crop of vesicles occurs. Therefore, patient-initiated therapy has been shown to be more effective than physician-initiated treatment plans.<sup>21</sup> Once the diagnosis has been made, patients should have access to the medication to initiate treatment after the earliest symptom. Patients with longer prodromes are easier to treat in this manner, as they have more time to be treated prior to lesion onset.

**Suppressive therapy.** Such therapy is indicated in patients with frequent attacks. Although the medical literature classifies “frequent” as six attacks per year, the definition of “frequent” is best assessed by the patient. Patients with severe disease, or cutaneous sequelae, may wish to be suppressed even if attacks are infrequent. Suppressive therapy is most commonly used in the first years of infection, as it is during this time that attacks will recur most frequently.

Evidence suggests that suppressive therapy can prevent or reduce the frequency of subsequent attacks.<sup>22</sup> It is crucial to remind patients to maintain condom use during suppressive therapy, as an “out of sight, out of

mind” attitude is highly likely. Because suppressive therapy also decreases subclinical shedding, it is therefore an appropriate treatment for the patient’s sexual partners as well.

### Potential medication side effects

In initial clinical trials, valacyclovir was utilized in high doses (8 g/day) for long periods (57 weeks) in severely ill patients to determine in vivo efficacy of the medication for treating cytomegalovirus. Thirty-three patients (3%) developed thrombotic thrombocytopenic purpura hemolytic uremia/anemia syndrome.<sup>23</sup>

Although this condition can occur spontaneously in all severely immunocompromised patients, the incidence in these studies vastly exceeded expected levels. As such, there is a bold box warning regarding its use in immunocompromised patients. In similar studies with 2-g to 3-g doses in HIV-infected patients, no similar events occurred, suggesting that this condition is dose dependent. Subsequently, the same warning was added to acyclovir, since valacyclovir is a pro-drug that becomes acyclovir intracellularly. There are no reports of similar occurrences with the use of famciclovir.

Other antiviral agents, such as foscarnet, have a higher incidence of adverse effects and are administered intravenously. Their use, therefore, is limited primarily to acyclovir-resistant patients. Resistance, which is unusual, is seen most often in HIV-infected patients.<sup>24</sup> One study reported the successful use of topical foscarnet in one HIV-infected, acyclovir-resistant patient.<sup>25</sup>

### Alternative treatments

Those turning to alternative methods of treatments may be disappointed with the options. Lysine is a commonly used alternative medication whose effectiveness

is touted by health food stores although no studies have been done to show its effectiveness in preventing or shortening herpes outbreaks. Harmful effects, however, are also not reported.

HSV immunization studies have been underway since the 1930s, but have yet to produce a clinically useful vaccine. Although existing medications are available to reduce disease symptomatology and frequency, it is likely that only a vaccine will be capable of halting the HSV-2 pandemic. Genital herpes is a disease in which vaccine-induced prevention is possible since subtype immunity appears to be protective.<sup>26</sup>

### HSV and concomitant medical conditions

**HIV infection.** HIV-infected patients have unique clinical courses with HSV-1 and HSV-2 that need to be specifically addressed. Among HIV-infected patients, 95% have either or both viral infections. Attacks tend to be longer, and of increased severity. Lesions may also not be self-limited, becoming large, chronic ulcerations. Secondary infections can result with *Staphylococcus* and *Streptococcus* being the most common causes. As mentioned previously, HSV ulcers will increase the transmission of other sexually transmitted infections. Therapy may require higher doses, more frequent dosing schedules, and longer treatment duration. Suppression may be harder to accomplish. Although these patients may be more difficult to treat, the consequences of non-treatment are more significant, therefore efforts should be made to suppress, as much as possible, both attacks and subclinical shedding.

**Pregnancy.** In pregnant women, distinguishing between primary and secondary attacks is of paramount importance. True first episodes of genital herpes during pregnancy have the highest risk of fetal and neonatal morbidity.<sup>27</sup> Since HSV infection is often asymptomatic, initial attacks during pregnancy may not be true primary episodes at all.<sup>28</sup> Although problems caused by genital herpes outbreaks in the early stages of pregnancy are uncommon, we should be seriously concerned about

the transmission of the virus to an HSV-incompetent baby in the third trimester. Titers of maternal antibodies are insufficient to prevent neonatal infection, which can be fatal.<sup>28</sup>

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### On the horizon: a herpes vaccine

The results of clinical studies of a new herpes vaccine were announced at last year's annual meeting of the American Society for Microbiology. The vaccine was more than 70% effective in preventing genital herpes in women with no previous exposure. It is produced by cloning key proteins on the surface of the virus. These proteins can prime the immune system to manufacture antibodies against the viruses.