Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection

Author
Mary A Albrecht, MD

Section Editor
Martin S Hirsch, MD

Deputy Editor
Jennifer Mitty, MD, MPH

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INTRODUCTION — Genital herpes simplex virus (HSV) infections are a major global public health problem:

- A dramatic upsurge in genital HSV infections has been documented from seroprevalence studies.
- There is a wide diversity of the clinical spectrum of genital HSV disease.
- Like all herpes virus strains, HSV establishes a latent state followed by viral reactivation and recurrent local disease.
- Perinatal transmission of HSV can lead to significant fetal morbidity and mortality.
- A link has been established between HSV-related genital ulcer disease and sexual transmission of HIV.

The epidemiology, varied clinical manifestations, and diagnosis of genital HSV infection will be reviewed here. The treatment of this disorder and issues related to genital herpes in pregnancy are discussed separately. (See "Treatment of genital herpes simplex virus infection" and "Prevention of genital herpes virus infections" and "Genital herpes simplex virus infection and pregnancy").

EPIDEMIOLOGY — Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are common infections worldwide. Both HSV-1 and HSV-2 can cause genital herpes, and infection of the same anatomic site by both HSV-1 and HSV-2 has been documented [1]. However, genital HSV is frequently under-recognized because infection is often subclinical [2-4].

Most cases of recurrent genital herpes are caused by HSV-2 [5,6]. From 2005 to 2010, the seroprevalence of HSV-2 in the United States was approximately 16 percent among patients aged 14 to 49 [7]. In one study that evaluated 7293 patients in this age group, the seroprevalence increased with age and number of sexual partners, and was greater among women compared with men (21 versus 12 percent) [8]. HSV-2 seroprevalence was also three times greater among non-Hispanic blacks (39 percent) than among non-Hispanic whites (12 percent). Similar risk factors for HSV-2 positivity have been noted in other surveys [3,9-13]. Prior HSV-1 infection does not appear to affect the rate of HSV-2 acquisition [14].

However, HSV-1 has been associated with an increasing proportion of cases of genital herpes infection, especially among young women and men who have sex with men [3,5,15-17]. As examples:

- Over a two-year follow-up of 1427 HIV-seronegative MSM in Australia, incidence rates for HSV-1 and HSV-2 infection were 5.9 and 1.5 cases per 100 person-years, respectively [17]. In a multivariate analysis, incident infection with HSV-1 was significantly associated with younger age and reports of insertive oral sex with casual partners.
- In a retrospective analysis of genital herpes isolates from a university student health service in the United States, HSV-1 was more commonly isolated in women than men, and the proportion of newly diagnosed HSV-1 genital infection had increased from 31 percent in 1993 to 78 percent in 2001 [16].
- Among 3438 HSV-seronegative women between the ages of 18 and 30 in the United States and Canada who were enrolled in the control arm of a herpes vaccine study and who were followed prospectively between 2003 and 2007, 183 became infected with HSV: 127 (3.7 percent) with HSV-1 and 56 (1.6 percent) with HSV-2 [3]. The rate of infection for HSV-1 was more than twice the rate for HSV-2 (2.5 versus 1.1 per 100 person-years, respectively). HSV-1 was more common than HSV-2 as a cause of genital mucosal infections.

It is estimated that the majority of genital herpes infections are transmitted by persons unaware that they have the infection, or are asymptomatic when transmission occurs [6]. As an example, in a population-based cross-sectional survey of adults living in New York City, nearly 28 percent were infected with HSV-2 and 88 percent had no prior knowledge of their diagnosis [4]. In addition, prior HSV-1 infection increases the likelihood of asymptomatic HSV-2 infection by threefold [14].
TYPES OF INFECTION — The clinical designations of genital herpes simplex virus (HSV) infection are: primary, nonprimary first episode, and recurrent (table 1):

Primary — Primary infection refers to infection in a patient without preexisting antibodies to either herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2).

Nonprimary — Nonprimary first episode infection refers to the acquisition of genital HSV-1 in a patient with preexisting antibodies to HSV-2 or the acquisition of genital HSV-2 in a patient with preexisting antibodies to HSV-1 (eg, an individual with prior orolabial herpes and subsequent development of an HSV-1 antibody response develops genital herpes due to HSV-2 exposure).

Recurrent — Recurrent infection refers to reactivation of genital HSV in which the HSV type recovered in the lesion is the same type as antibodies in the serum.

Each of these types can be either symptomatic or asymptomatic (also called subclinical). Asymptomatic infection will be detected only if the patient is tested by culture or polymerase chain reaction (PCR).

TRANSMISSION — Transmission of herpes simplex virus (HSV) may occur quickly in new sexual relationships. In a prospective study of 199 patients with newly acquired HSV genital infection, the median duration of the sexual relationship was 3.5 months (range 1.5 to 10 months) and the median number of sex acts before transmission was 40 [18]. Condom use was infrequent (50 percent during first intercourse; 20 percent during last intercourse before diagnosis). The median time to infection was greater in participants whose partners informed them that they had genital herpes than in those whose partners did not (270 versus 60 days).

Transmission may also occur during periods of subclinical viral shedding (eg, when symptoms are absent). (See 'Viral shedding' below.)

CLINICAL FEATURES — The clinical manifestations of genital herpes simplex virus (HSV) vary widely depending upon whether the infection is primary, nonprimary or recurrent.

Primary infection — The clinical manifestations of primary genital HSV infection are highly variable [19,20]. The initial presentation can be severe with painful genital ulcers, dysuria, fever, tender local inguinal lymphadenopathy, and headache. In other patients, however, the infection is mild, subclinical, or entirely asymptomatic [12,19]. There are no clear differences in clinical presentation based on infecting virus (ie, HSV-1 versus HSV-2) [3].

The average incubation period after exposure is four days (range two to twelve days) [20]. In one review, patients with primary infections usually had multiple, bilateral, ulcerating, pustular lesions which resolved after a mean of 19 days [19]. Symptoms tended to be more severe in women than in men. Other symptoms and signs in these first episode infections included:

- Systemic symptoms, including fever, headache, malaise, and myalgias (67 percent)
- Local pain and itching (98 percent)
- Dysuria (63 percent)
- Tender lymphadenopathy (80 percent)

The clinician should differentiate dysuria from acute urinary retention, which can occur during severe primary HSV infection. Dysuria can lead to reluctance to void because of the passage of acidic urine on open and inflamed vesicles; this is best managed with Sitz baths. However, acute urinary retention with loss of sacral sensation can occur due to lumbosacral radiculomyelitis secondary to severe primary HSV infection [21]. This complication is transient, but usually requires catheterization until clinical improvement ensues.

Primary genital herpes is commonly associated with viremia; of 164 adults with confirmed primary genital HSV infection, 40 (24 percent) had HSV DNA detected in plasma [22]. In one study, virus was isolated most commonly from the urethra and cervix of women with first episode infection (82 and 88 percent, respectively) [19]. Viral isolation was less frequent from the urethra in men (28 percent) and the pharynx in either women or men (13 and 7 percent, respectively).

Nonprimary infection — Nonprimary first episode infection is associated with fewer lesions and less systemic symptoms than primary infection, presumably because antibodies against one HSV type offer some protection against the other [19,20]. In one study, prior HSV-1 infection increased the likelihood of asymptomatic infection three-fold [14].
**Recurrent infection** — Clinical recurrences of genital HSV are common, but are typically less severe than primary or nonprimary infections. The mean duration of lesions is generally shorter with recurrences than in primary infection (10 versus 19 days) and the duration of viral shedding is usually two to five days [12,19,23].

In one study that included a subset of 362 patients with recurrent infection, lesions were described as unilateral small vesicular or ulcerative lesions [19]. Atypical vaginal lesions include fissures or vulvar irritation. Systemic symptoms are infrequent and approximately 25 percent of recurrent episodes are completely asymptomatic [19]. As many as 50 percent of patients with symptomatic recurrences have prodromal symptoms before eruption such as local mild tingling or shooting pains in the buttocks, legs, and hips [20].

Factors that contribute to decreased recurrences include infection with HSV-1 compared to HSV-2 and the duration and severity of the primary infection [12]. Treatment with acyclovir does not influence recurrence rates [2].

**EXTRAGENITAL COMPLICATIONS** — Extragential complications occur in a minority of patients who present with primary herpes simplex virus (HSV) infection. In one study, extragenital complications included aseptic meningitis (8 percent), urinary bladder retention due to sacral autonomic nervous system dysfunction (2 percent), and distant skin lesions (20 percent) [19]. Other series have noted higher rates of aseptic meningitis (25 percent) and urinary retention syndromes (10 to 15 percent) in women with primary infection [12]. Transverse myelitis has been reported in immunosuppressed patients. (See 'Immunosuppressed patients' below.)

**Meningitis** — In patients with HSV meningitis, the cerebrospinal fluid (CSF) profile includes a pleocytosis (median white cell count 300 to 400/mm^3^) with a predominance of lymphocytes, and a normal CSF glucose concentration, although hypoglycorrhachia has been reported [19]. HSV has been isolated from 0.5 to 3 percent of CSF samples from patients with aseptic meningitis. (See 'Aseptic meningitis in adults'.)

HSV-2 can also cause recurrent episodes of meningitis, called Mollaret's meningitis. Most patients do not have evidence of genital lesions at the time of presentation. (See "Aseptic meningitis in adults", section on 'Herpes simplex meningitis' and "Aseptic meningitis in adults", section on 'Recurrent (Mollaret's) meningitis'.)

**Proctitis** — HSV can also cause proctitis, particularly in men who have sex with men (MSM). The differential diagnosis of proctitis in MSM includes N. gonorrhoeae, herpes simplex virus, and Treponema pallidum infections. The frequency of these causes was evaluated in a review of 101 episodes of proctitis among MSM in San Francisco; anoscopy was performed and specimens obtained that were tested for the above organisms [24]. The following etiologies were noted in 55 percent of cases with a confirmed diagnosis:

- Gonorrhea (20 percent)
- Herpes simplex (13 percent)
- Chlamydia (11 percent)
- Mixed infections (10 percent, including 3 percent with herpes)
- Syphilis (1 percent)

**FREQUENCY OF RECURRENCES** — Patients with primary genital herpes simplex virus (HSV) need to be counseled that recurrence is expected. The frequency of recurrence depends on the severity and duration of the initial episode, the infecting serotype, and the host.

In one series of 457 patients with HSV-2 primary infection, 89 percent had one recurrence during a follow-up of 391 days [2]. Furthermore, 38 percent of patients had as many as six recurrences and 20 percent had more than ten. Patients with primary infection lasting for five or more weeks experienced recurrences earlier and almost twice as often compared to those with a shorter duration of the initial infection.

Recurrent infection is more common with HSV-2 than HSV-1 [23,25]. The magnitude of this effect was evaluated in a prospective study of 137 patients with a first symptomatic episode of genital herpes [25]. The likelihood of recurrence was much higher with HSV-2 infections (60 versus 14 percent with HSV-1). As a result, the proportion of episodes due to HSV-1 fell from 15 percent in primary first episodes to 2 percent in recurrent episodes.

Reurrences are also more common in immunosuppressed patients. (See "Immunosuppressed patients" below.)

**VIRAL SHEDDING** — After resolution of the primary genital herpes simplex virus (HSV) infection, asymptomatic intermittent viral shedding occurs in both men and women, even in the absence of genital lesions [13,26-29]. A
prospective study of 498 immunocompetent HSV-2-seropositive persons demonstrated that HSV was shed more frequently in the 410 symptomatic persons compared with the 88 asymptomatic persons (20 percent versus 10 percent of days), although the quantities of virus were similar between the two groups [29]. HSV genital shedding can also occur during a clinical outbreak primarily affecting the buttock region, which may reflect reactivation from sacral neural ganglia [30]. Subclinical HSV shedding is important since infection can be transmitted unknowingly to susceptible sexual partners and neonates. (See ‘Sex partners’ below and “Genital herpes simplex virus infection and pregnancy”.)

The frequency of shedding is influenced by the infecting serotype, whether the infection is primary or nonprimary and the duration of time since the first clinical episode.

- Primary genital HSV-2 infections have been linked to more frequent and prolonged asymptomatic viral shedding from the genitourinary tract compared to HSV-1 infections [15,23,25].
- In one study of 110 women with a median follow-up period of 105 days, viral shedding occurred on a mean of two percent of days, most often within seven days of a symptomatic recurrence, and was more likely to occur in patients with HSV-2 or mixed HSV-1 and HSV-2 infections compared to HSV-1 alone (55 and 52 versus 29 percent of patients) [23].
- A lower frequency of subclinical infection was noted in a cohort study of 306 women with a first episode of genital HSV infection [31]. Asymptomatic viral shedding was detected among 18, 23, and 12 percent of women with primary HSV-2, nonprimary HSV-2, and primary HSV-1 genital infections, respectively. Asymptomatic cervical viral shedding was three times more frequent during the first three months following resolution of primary HSV-2 disease than at later time points and was consistently more common in patients with HSV-2 compared to HSV-1 genital infections.
- Time since the first genital HSV episode was significantly associated with reduced genital shedding in a study of 377 adults who self-collected anogenital swabs for HSV-2 DNA for a minimum of 30 consecutive days [32]. The frequency of subclinical HSV shedding occurred in 26 percent of days among patients infected less than one year to 9 percent of days among those infected for more than 10 years. Although the frequency of subclinical shedding decreased, the quantity of virus remained stable over time, which may be associated with continued risk for transmission.

SEX PARTNERS — Several studies have evaluated the risk of sexual transmission of genital herpes from index patients with recurrent herpes simplex virus (HSV) genital disease to susceptible partners [33,34]. In one report, 144 heterosexual couples, in which the source partner had symptomatic recurrent genital HSV, were evaluated over a median of 334 days for development of culture-confirmed HSV infection or type-specific antibodies in the susceptible partner [33]. The following findings were noted:

- Transmission of genital HSV was documented in 14 couples (10 percent); the risk was greater with male than with female source partners (17 versus 4 percent).
- In susceptible women who lacked HSV-1 and HSV-2 antibodies at entry, the rate of acquiring genital herpes infections was higher than in women with preexisting HSV-1 antibodies (32 versus 9 percent)
- In 70 percent of patients, transmission of genital herpes was linked to sexual contact during periods of asymptomatic viral shedding. (See ‘Viral shedding’ above.)

A second smaller study confirmed these findings of a greater risk of HSV acquisition with male source partners and in patients without HSV antibodies [34].

A more detailed discussion of how to prevent transmission of HSV to sex partners is found elsewhere. (See “Prevention of herpes simplex virus type 1 infection in immunocompetent patients”, section on ‘Prevention of sexual transmission’.)

IMMUNOSUPPRESSED PATIENTS — Most genital herpes simplex virus (HSV) infections occurring in immunosuppressed adults reflect reactivation syndromes. The clinical presentation of symptomatic episodes may include extensive mucocutaneous involvement, variable appearance of genital lesions, and the development of chronic and recurrent ulcers. Recurrences are often more frequent, more extensive, and of longer duration than in immunocompetent patients [35,36]. In addition, immunosuppressed patients may have prolonged viral shedding.
A prospective trial evaluated 217 HIV-infected women who underwent twice yearly pelvic examination, including cultures of cervicovaginal specimens and swab specimens from genital lesions, if lesions were present [37]. The following findings were noted:

- One-third had genital HSV-2 infection based upon history alone or positive culture results.
- Among these women, an HSV-2 culture was positive in one-third of visits; a positive culture was not associated with an apparent genital lesion approximately one-third of the time.
- Positive cultures occurred more frequently in patients with lower CD4 cell counts and higher plasma HIV-1 RNA levels. However, in one study, even optimum CD4 gains and viral suppression with ART did not eliminate the risk of significantly more genital lesions in HIV-infected women compared to controls [38].

In addition to genital symptoms, neurologic complications occasionally develop and rapidly evolve in the setting of genital and mucocutaneous HSV infection occurring in transplant recipients and in HIV-infected patients with advanced disease. These complications include aseptic meningitis, sacral radiculopathy, and transverse myelitis [39-41].

**PREGNANCY** — Genital herpes simplex virus (HSV) infection is of particular concern in pregnant women because of the risk of transmission to the infant during delivery. This issue is discussed elsewhere. (See "Genital herpes simplex virus infection and pregnancy".)

**HSV-2 AND RISK OF HIV TRANSMISSION** — Herpes simplex virus type 2 (HSV-2) genital ulcer disease has been definitively linked to an increased risk for acquisition of HIV-1 infection in regions with high seroprevalence rates of HSV-2 infection [42-52].

**Epidemiology** — A 2002 meta-analysis of 31 studies was undertaken to assess the risk of acquiring HIV infection in HSV-2 seropositive individuals [45]. Depending upon the type of study, the risk estimate in HSV-2 seropositive individuals varied from 2.1 (95% CI 1.4-3.2) to 3.9 (95% CI 3.1-5.1). However, the temporal sequence of the two infections could not be determined.

In a subsequent meta-analysis, 18 longitudinal studies were selected in which the relative timing of HSV-2 and HIV infections could be determined [53]. This study demonstrated that prevalent HSV-2 infection was associated with a three-fold increased risk of HIV acquisition among both men and women in the general population. Modeling studies also demonstrate that HSV-2 epidemics could theoretically double the peak HIV incidence and create a "core group" of HIV transmitters in areas where HSV is highly prevalent [49].

Subsequent studies have underscored the relative importance of recent HSV infection, as compared to remote HSV infection, as a risk factor for HIV acquisition [44,50,54]. In a pivotal seroepidemiologic study conducted in India, a cohort of 2732 HIV-seronegative patients (17 percent female) followed at sexually transmitted disease (STD) and reproductive tract clinics underwent HSV-2 antibody screening at baseline and were prospectively followed to assess for seroconversion to HIV-1 and HSV-2 [44]. The prevalence of HSV-2 at the time of enrollment was 43 percent, almost one-half of whom reported no history of genital ulcer disease. The following findings were noted during follow-up:

- The incidence of HSV-2 and HIV infection was 11.4 cases and 5.8 cases/100 person-years, respectively.
- The risk of acquiring HIV infection in this cohort was 3.6 percent for HSV-2 seronegative individuals at baseline, 7.5 percent for individuals with positive HSV-2 serology at baseline, and 22.6 percent for individuals with confirmed recent HSV-2 seroconversion within the past 6 months. The adjusted hazard ratios for HIV infection were 1.67 for HSV-2 infection at study entry, 1.92 for remote incident HSV-2 infection, and 3.81 for recent incident HSV-2 infection.

This association between HIV acquisition and HSV infection, particularly recent HSV infection, was confirmed in a nested case-control study in Tanzanian patients attending STD clinics [50].

These findings underscore the need for effective HSV-2 interventions when implementing infection control strategies designed to limit HIV transmission. Clinical trials evaluating the impact of antiviral treatment of HSV-2 infected individuals with acyclovir or valacyclovir on the incidence of HIV sexual transmission may provide pivotal information about how to implement interventional therapies on a global scale [49,51,55]. There is also promising data on the use of an intravaginal gel that has antiviral activity against both HIV and HSV [56].
Mechanisms — At least three mechanisms may be important for the increase in HIV-1 transmission associated with sexual activity in patients with HSV-2 infection:

- Symptomatic HSV-2 genital ulcers frequently cause local inflammation and mucosal disruption in the genital tract, which can facilitate HIV-1 entry during exposure to HIV-infected genital fluids [26].
- Genital HSV-2 ulcers selectively increase local recruitment of CD4 positive cells, which may serve as targets for HIV-1 attachment in mucosal tissue [57,58].
- Replication competent virus has been isolated in HSV-2 lesions [42].

Differential Diagnosis — Among patients with genital herpes who present with a genital ulcer, the primary differential diagnosis includes syphilis and chancroid among infectious causes, and drug eruptions and Behçet's syndrome among noninfectious causes. (See "Approach to the patient with genital ulcers".)

A diagnosis based upon history and physical examination alone is often inaccurate [6]. Therefore, the clinical diagnosis of genital herpes should be confirmed by laboratory testing. Nonetheless, some findings are more common in certain infections [59].

- The classic presentation of genital herpes is with multiple, shallow, tender ulcers that may be vesicular; in addition, only herpes simplex virus (HSV) is associated with recurrent disease.
- The classic genital presentation of primary syphilis is with a painless, indurated, clean-based ulcer, called a chancre.
- The classic genital presentation of chancroid is with a deep, undermined, purulent ulcer that may be associated with painful inguinal lymphadenitis. (See "Chancroid".)

Diagnosis — A clinical diagnosis of genital herpes should be confirmed with laboratory testing [60]. The classical presentation with multiple vesicles on an erythematous base is often absent in many patients. Thus, it is important to confirm the diagnosis of herpes simplex virus (HSV) infection with either of the following techniques: viral culture, polymerase chain reaction (PCR), direct fluorescence antibody, and type-specific serologic tests. The choice of test varies with the clinical presentation [60]. Cell culture and PCR-based testing are the preferred tests for a patient presenting with active lesions, although PCR-based testing has the greatest overall sensitivity and specificity.

Viral Culture — If active genital lesions are present, the vesicle should be unroofed for sampling of vesicular fluid for culture. However, the overall sensitivity of viral culture of genital lesions is only approximately 50 percent [61,62]. The diagnostic yield of culture is highest in the early stages of disease, when lesions are typically vesicular, and declines rapidly as the lesions begin to heal [63]. Viral isolation rates are also higher with primary compared to recurrent genital herpes, particularly in the setting of asymptomatic recurrences with subclinical shedding.

Specimens for culture should be directly placed in viral culture media and rapidly transported to the laboratory. Viral isolates usually grow in tissue culture by five days and are typed by antibody staining.

Polymerase Chain Reaction — While viral culture has remained the standard diagnostic method for isolating HSV, real-time HSV PCR assays have emerged as a more sensitive method to confirm HSV infection in clinical specimens obtained from genital ulcers and mucocutaneous sites; PCR is the test of choice for cerebrospinal fluid [6,64-67].

PCR is particularly useful for the detection of asymptomatic HSV shedding. It has also been used in clinical studies to evaluate the risk of transmission in discordant couples and the effectiveness of suppression with antiviral therapy [68,69]. (See "Treatment of genital herpes simplex virus infection".)

The enhanced sensitivity of HSV PCR compared to viral culture can be illustrated by the following observations from different studies:

- HSV DNA levels with PCR testing were 250 times higher from culture-positive compared to culture-negative samples [70].
- Among women with recurrent genital herpes who underwent daily sampling of genital lesions, HSV DNA was detected in ulcerative lesions on 15 of 17 days compared to only 3 of 17 days by viral isolation [68].
- A randomized trial compared valacyclovir, acyclovir, and placebo for suppression of HSV shedding in the genital tract [69]. During the placebo period, both the lesional HSV shedding rate (87 versus 47 percent of days) and the asymptomatic shedding rate (27 versus 7 percent of days) were significantly higher with PCR than with
culture. The higher sensitivity of PCR compared to culture was also confirmed in the treatment phase of the study.

Earlier diagnosis by real-time HSV PCR assays may also reduce the transmission of infection during reactivation syndromes that are manifested only by asymptomatic viral shedding [61,63,70].

Further development of this assay now allows differentiation of HSV-1 and HSV-2 using real-time TaqMan PCR techniques [71]. A limiting factor in adopting real-time HSV PCR as the primary diagnostic tool in many clinical reference laboratories is the cost of the assay, which substantially exceeds that of viral culture.

**Direct fluorescent antibody** — Many diagnostic laboratories provide a rapid type-specific direct fluorescent antibody (DFA) test to detect HSV in clinical specimens. This test is specific and reproducible.

**Serology** — Type specific antibodies to HSV develop during the first several weeks after infection and persist indefinitely [6]. The availability of type-specific antibody testing has facilitated greater accuracy in epidemiologic surveys. (See ‘Epidemiology’ above.)

**Interpretation and use of serologic testing** — Several FDA-approved type-specific HSV serologic tests are commercially available to clinicians evaluating genital ulcer disease in adults [72-74]. Serologic testing for HSV-1 and HSV-2 can be used to [6,72,73]:

- Diagnose a patient with a history of genital lesions who did not have a diagnostic workup, or had a negative HSV culture or PCR.
- Diagnose a past or present HSV infection in a patient with an atypical presentation.
- Determine susceptibility of a sexual partner of a patient with documented genital HSV infection.
- Identify asymptomatic HSV infection in pregnant women who are at risk for shedding at the time of delivery with potential transmission to the infant. (See “Genital herpes simplex virus infection and pregnancy”.)
- Help predict the risk of recurrence. (See ‘Frequency of recurrences’ above.)

The availability of type-specific serology using surface glycoproteins (gG2 and gG1 for HSV-2 and HSV-1, respectively) to distinguish HSV-1 and HSV-2 enables the clinician to determine if the patient is at risk of acquisition or has evidence of prior infection with either subtype [27,75]. A positive serology indicates present or past infection; IgM antibody testing is not useful for discriminating primary versus recurrent episodes of HSV infection. Since genital ulcers have many possible etiologies, a positive HSV IgG antibody serology cannot be used for diagnosis of an active genital ulcer without further diagnostic evaluation. In contrast, a positive culture for HSV in a HSV seronegative patient is strong evidence of primary infection [60]. Positive serologic testing for HSV-2 indicates anogenital infection, but positive serologic testing for HSV-1 can be consistent with either anogenital or orolabial infection. (See “Approach to the patient with genital ulcers”.)

**Types of serologic testing**

- Surface glycoproteins — The sensitivities of glycoprotein G type-specific tests vary from 80 to 98 percent and false negative results may occur at early stages of infection [6].
- Rapid serologic testing — The rapid test has a sensitivity and specificity of 97 and 98 percent, respectively, and positive and negative predictive values of 92 and 99 percent, respectively [76]. Rapid testing can be completed in 15 minutes at the point of care. Rapid serologic testing may be useful in developing countries where HSV-2 prevalence is high and resource limitations preclude other types of laboratory testing [77].

**Tzanck smear** — The Tzanck smear, which may demonstrate the cytopathic effect of the virus (multinucleate giant cells), can be performed on lesion scrapings from patients with active genital lesions. However, it has limited utility since it has low sensitivity and specificity and is only helpful if positive [78]. Furthermore, only a viral culture or PCR-based testing can determine whether the infection is due to HSV-1 or HSV-2.

**SCREENING** — The relatively high seroprevalence rate of herpes simplex virus type 2 (HSV-2) infection in the United States (22 percent in persons ≥12 years of age between 1988 and 1994) [11] and the risk of transmission to sexual partners has raised the question of whether serologic screening may be justified in asymptomatic sexually active individuals. At present, routine screening for HSV-2 is not recommended because there may be a relatively high false positive rate in low risk populations, which could create uncertainty in the absence of formal guidelines about how to reconcile the test results [6,79].
Issues related to the possible role of screening in pregnant women are discussed separately. (See "Genital herpes simplex virus infection and pregnancy").

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Genital herpes (The Basics)")
- Beyond the Basics topics (see "Patient information: Genital herpes (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

- Herpes simplex virus (HSV) is a common sexually transmitted disease worldwide. Although HSV-2 has historically been the main causative agent for the preponderance of virologically confirmed infections, HSV-1 is associated with an increasing proportion of cases of genital herpes. (See 'Epidemiology' above.)
- The clinical designations of genital HSV infection are: primary, nonprimary first episode, and recurrent infection. Primary infection refers to infection in a patient without preexisting antibodies to either HSV-1 or HSV-2. Nonprimary first episode infection refers to the acquisition of genital HSV-1 in a patient with preexisting antibodies to the alternate serotype. Recurrent infection refers to reactivation of genital HSV in which the HSV type recovered in the lesion is the same type as those seen on serologic testing. (See 'Types of infection' above.)
- Transmission of HSV may occur quickly in new sexual relationships. (See 'Transmission' above.)
- The clinical manifestations of primary genital HSV infection are highly variable. The initial presentation can be severe with painful genital ulcers and constitutional symptoms; in other patients, the infection may be mild or entirely asymptomatic. (See 'Clinical features' above.)
- Nonprimary first episode infection is associated with fewer lesions and less systemic symptoms than primary infection, presumably because antibodies against one HSV type offer some protection against the other. (See 'Nonprimary infection' above.)
- Clinical recurrences of genital HSV are common, but are typically less severe than primary or nonprimary infections. (See 'Recurrent infection' above.)
- Extragenital complications, like aseptic meningitis and urinary retention, occur in a minority of patients who present with primary HSV infection. (See 'Extragenital complications' above.)
- The frequency of recurrence depends on the severity and duration of the initial episode, the infecting serotype, and the host. (See 'Recurrent' above.)
- After resolution of the primary genital HSV infection, asymptomatic intermittent viral shedding has been documented in both men and women in the absence of genital lesions. Subclinical HSV shedding is important since infection can be transmitted unknowingly to susceptible sexual partners and neonates. (See 'Viral shedding' above.)
- Among susceptible sexual partners, there is a greater risk of HSV acquisition with male source partners and in patients without HSV antibodies. (See 'Sex partners' above.)
- In immunosuppressed patients, most genital HSV infections occurring in immunosuppressed adults reflect reactivation syndromes. Symptomatic episodes may more severe, frequent, and longer in duration. (See 'Immunosuppressed patients' above.)
- HSV-2 genital ulcer disease has been definitively linked to an increased risk for acquisition of HIV-1 infection in regions with high seroprevalence rates of HSV-2 infection. (See 'HSV-2 and risk of HIV transmission' above.)
- The diagnosis of HSV infection can be confirmed by polymerase chain reaction (PCR), viral culture, and type-specific serologic tests. The choice of test varies with the clinical presentation. PCR-based assays or culture are
preferred for active genital lesions; serologic testing is the preferred method in patients without active disease.

- Routine screening for HSV-1 or HSV-2 infection by serologic testing is not recommended. (See 'Screening' above.)

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REFERENCES


Clinical designation of genital herpes simplex virus infection (HSV)

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* This occurs extremely rarely.
INTRODUCTION — Genital herpes simplex is a common sexually transmitted virus infection that is found worldwide. Most of these genital infections are caused by herpes simplex virus-2 (HSV-2), but herpes simplex virus-1 (HSV-1) also produces a clinically similar disease. Antiviral therapy can shorten the duration of symptoms and signs in primary infection which, when untreated, can be associated with significant morbidity. Clinical recurrences are also common and can be treated episodically or prevented with continual antiviral suppression.

This topic review addresses the natural history of genital HSV infection, clinical recurrences, and data supporting treatment efficacy of primary and repeated episodes of infection. The epidemiology, clinical manifestations, and diagnosis of genital HSV infection and issues related to pregnancy are presented separately. (See "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection" and "Genital herpes simplex virus infection and pregnancy" and "Prevention of genital herpes virus infections".)

NATURAL HISTORY OF INFECTION

Primary infection — An HSV outbreak is defined as “primary” if the patient was HSV-seronegative for both HSV-1 and HSV-2 before the episode of genital lesions. The primary episode of genital HSV infection can be associated with a multitude of constitutional symptoms and signs, such as fever, malaise, and headache. In addition to painful genital lesions, dysuria can be severe. Symptoms may last two to four weeks if left untreated. (See "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection" and "Genital herpes simplex virus infection and pregnancy".)

Nonprimary infection — Nonprimary episode infection refers to HSV-2 infection in a person with preexisting HSV-1 immunity [1]. The signs and symptoms of nonprimary infection tend to be less severe than in the person without any existing HSV antibodies.

Recurrent symptomatic disease — Although treatment during primary infection lessens morbidity, it does not eradicate latent virus, which can subsequently reactivate. Genital HSV infection often leads to frequent clinical recurrences, although the risk of genital recurrence is lower in those infected with HSV-1 versus HSV-2 [2]. In the absence of suppressive antiviral therapy, the median recurrence rate after the first episode of HSV-2 infection is about four recurrences a year, with about 40 percent of patients having at least six recurrences and 20 percent having more than 10 recurrences in the first year [1,3]. In contrast, recurrences of HSV-1 occur much less frequently (approximately once per year). Over time, recurrences due to either viral type generally decrease in number and severity, although there is substantial variability in the clinical course from patient to patient [3,4].

With recurrent infection, genital lesions may be asymptomatic, few in number, or atypical in appearance, especially in women (eg, fissures or vulvar irritation). In addition, the mean duration of lesions is shorter than that seen with the primary episode (10 versus 19 days) and the duration of viral shedding is shorter (two versus nine days) [5]. Finally, antiviral therapy does not eradicate latent HSV infection and thus does not change the frequency or severity of recurrences, once therapy is stopped [1,2,4]. (See "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection", section on 'Recurrent infection'.)

These concepts were well illustrated in an observational cohort study of 664 immunocompetent patients with genital HSV-1 or HSV-2 infection who were followed for a minimum of 14 months; 306 had newly-acquired infection [4]. The following findings were noted:

- Among patients with newly acquired genital herpes, the median rate of recurrence in the first year was lower in patients with HSV-1 compared with HSV-2 infection (one versus five per year, respectively). Second year rates were lower in both groups.
Patients infected with HSV-2 who were followed for more than four years had a decreased recurrence rate over time. However, about one-fourth of patients experienced an increase in recurrences at the five-year follow-up, highlighting the variability in disease course among HSV-2-infected persons.

**ANTIVIRAL AGENTS** — As discussed in detail in the next section, acyclovir, famciclovir, and valacyclovir appear to have similar efficacy for the treatment of primary genital herpes and for the suppression of recurrent infection [6,7]. Famciclovir and valacyclovir have greater oral bioavailability than acyclovir. Topical therapy is of marginal benefit and should not be used [8]. The margin of safety and tolerability of all three medications is excellent. (See "Acyclovir: An overview").

**TREATMENT OF PRIMARY HSV** — Primary HSV infection can cause prolonged clinical illness with severe genital ulcerations. Thus, all patients with a suspected primary episode of HSV should be treated with antiviral therapy. Initiation of oral antiviral therapy within 72 hours of lesion appearance may decrease duration and severity of illness by days to weeks [9]. Furthermore, antiviral therapy can decrease the risk of complicated primary infection (eg, meningitis or sacral radiculitis) [10]. (See 'Complicated HSV' below.)

All of the available agents (ie, acyclovir, famciclovir and valacyclovir) are efficacious in the treatment of primary genital HSV infection. The dosing frequency varies from agent to agent. Multiple trials have been conducted to determine the shortest duration of therapy that may be effective in achieving symptomatic relief. Oral therapy is usually adequate, except in cases of complicated HSV infection. (See 'Complicated HSV' below.)

The following is a survey of the major clinical trials that have assessed the efficacy of antiviral therapy.

**Acyclovir versus placebo** — Most data on the treatment of primary genital herpes come from studies with acyclovir [5,11]. As an example, in a randomized, controlled trial, 48 patients with a first episode of genital herpes were assigned to acyclovir (200 mg) or placebo five times daily for ten days [11]. Acyclovir significantly reduced pain, length of time to healing, and duration of viral shedding. Similar benefits, including resolution of constitutional symptoms, were associated with acyclovir use in another placebo-controlled trial [5].

**Famciclovir versus acyclovir** — Famciclovir, the oral prodrug of penciclovir, has increased bioavailability as well as a substantially longer half-life compared with acyclovir. This allows for less frequent dosing of famciclovir compared with acyclovir.

Famciclovir and acyclovir have comparable efficacy for the treatment of primary genital HSV. In three separate double-blind controlled studies, several different dosing regimens of famciclovir (125, 250, 500, 750 mg) were compared with acyclovir for either 5 or 10 days of dosing in a total of 951 patients; one-third of the enrolled patients had primary HSV [12]. Famciclovir was given three times daily and acyclovir was given five times daily. Duration of shedding, median time to lesion healing, and time to resolution of symptoms were comparable among the famciclovir and acyclovir arms. In the 10-day study, the 125 mg famciclovir arm was not as effective as the other doses.

**Valacyclovir versus acyclovir** — Valacyclovir and acyclovir appear equally efficacious, although valacyclovir affords less frequent dosing. In a large multicenter, comparative, randomized trial, 643 adults with a first episode of genital herpes were assigned to 10 days of therapy with acyclovir (200 mg PO five times daily) or valacyclovir (1000 mg PO twice daily) [13]. There were no significant differences between the regimens in time to healing, duration of pain, time to clearing of all symptoms, and duration of viral shedding.

**Valacyclovir versus famciclovir** — No studies have directly compared these two agents for the first episode of genital HSV infection.

**Complicated HSV** — Parenteral therapy may be required in patients with primary genital herpes infections accompanied by more severe clinical manifestations, such as [14]:

- Central nervous system disease, such as aseptic meningitis, encephalitis, or transverse myelitis
- End organ disease including hepatitis or pneumonitis
- Disseminated HSV

The dose of IV acyclovir and the specific duration of therapy are not well delineated based on a lack of clinical trials; treatment should be individually tailored to the specific clinical setting. In patients with complicated HSV infection, the Centers for Disease Control and Prevention (CDC) recommends intravenous acyclovir (5 to10mg/kg every eight hours for two to seven days or longer until clinical improvement is documented, followed by transition to oral antiviral therapy.
to complete at least 10 days of therapy) [14]. (See "Aseptic meningitis in adults", section on 'Herpes simplex meningitis' and "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection", section on 'Extragential complications'.)

Immunocompromised patients may have a more severe and protracted course and may require longer therapy.

**Adjunctive therapy for primary HSV** — Some patients with a primary episode of genital HSV experience moderate to severe local pain in the affected genital or sacral areas. Analgesics may be required in severe primary episodes with multiple painful lesions. Sitz baths are often helpful for women with severe dysuria secondary to multiple ulcerations.

A woman who complains of difficulty urinating may have developed urinary retention secondary to sacral nerve root involvement. In this clinical situation, either intermittent or indwelling bladder catheterization may also be required, usually for several days, but occasionally extending beyond one week. Administration of pain medications prior to catheter insertion helps to decrease discomfort associated with the procedure.

**Timing of initiation of therapy** — Prompt initiation of therapy is important to obtain maximal clinical benefit. Most studies have evaluated drug initiation within 72 hours of onset of clinical symptoms; however, if a patient presents after this time frame with ongoing development of new lesions and significant pain, antiviral therapy should still be offered.

**Summary for primary genital HSV treatment** — Compared with untreated disease, oral antiviral therapy significantly decreases the duration and severity of disease with minimal adverse drug effects. We therefore recommend oral antiviral therapy for the treatment of uncomplicated primary genital HSV infection. Any of the three available agents can be used in this setting, since they all appear equally effective [14-17]. **Valacyclovir** is dosed less frequently than **acyclovir** and **famciclovir**, whereas **acyclovir** is much less expensive. The usual duration of treatment is 7 to 10 days.

We agree with the 2015 Centers for Disease Control and Prevention guidelines, which recommend the following oral treatment options [14]:

- **Acyclovir**: 400 mg three times daily or 200 mg five times daily
- **Famciclovir**: 250 mg three times daily
- **Valacyclovir**: 1000 mg twice daily

**TREATMENT STRATEGIES FOR RECURRENT DISEASE**

**Therapeutic options** — For patients with recurrent genital HSV, factors that influence the management strategy include the frequency of recurrent episodes, severity of symptoms and signs, and risk of viral transmission to an uninfected sexual partner. Clinicians and patients alike need to also be aware that viral shedding can occur despite complete absence of symptoms. (See "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection", section on 'Viral shedding'.)

Specific options include the following:

- **Chronic suppressive therapy**: This strategy involves the administration of daily antiviral therapy, which may be most appropriate for those with very frequent recurrences or HSV-seropositive patients with uninfected sexual partners.
- **Episodic therapy**: This approach involves self-administered antiviral therapy for individual outbreaks as they arise. Patients should be counseled to start therapy at the very first sign of prodromal symptoms (eg, tingling, paresthesias, pruritus), which may occur prior to onset of discrete lesions.
- **No intervention**: No therapeutic intervention may be appropriate for some patients, particularly those with infrequent episodes and/or minimal symptoms.

**Comparisons between episodic and suppressive therapy** — There are limited data on the optimal treatment strategy, each of which has its advantages and disadvantages.

**Clinical benefits** — One early placebo-controlled trial of **acyclovir** in 156 patients with frequent recurrences (more than six per year) compared suppressive therapy (400 mg twice daily) to episodic therapy (200 mg five times daily) for five days [18]. The trial results demonstrated that suppressive therapy was superior compared with the other arms in:
Increasing the median time to recurrence (250, 28, and 23 days for patients in the suppressive, episodic, and placebo arms, respectively).

Reducing the median number of days per month with active disease (0.32, 4.18 and 4.72 days for the suppressive, episodic, and placebo arms, respectively).

Quality of life — Quality of life measures appear to be superior with chronic suppressive therapy [19,20]. This was shown in a multicenter, open-label, randomized, two-arm, crossover study involving 225 patients, in which the role of valacyclovir for episodic (500 mg twice daily for five days) versus suppressive therapy (500 mg daily) was evaluated [20]. The mean number of recurrences prior to study entry was approximately six per year. The study demonstrated the following results:

- The probability of developing a recurrence was 78 percent lower in patients assigned to the suppressive therapy arm than to the episodic arm.
- No serious drug toxicity was reported over the 48-week period of the study.
- Of the 202 patients who completed the 48-week study, patient preference strongly favored suppressive versus episodic therapy (72 versus 28 percent). Treatment satisfaction (as measured by a disease-specific validated questionnaire) was based on various factors, such as perceived drug effectiveness, convenience, and lifestyle effects.

Patient considerations — The choice of episodic versus chronic suppressive therapy should also be individualized based on patient preference [21].

Frequency of recurrences — For patients with recurrent HSV, decisions regarding suppressive versus episodic therapy are strongly influenced by the frequency and severity of the clinical episodes.

Adherence — Some patients may find chronic suppressive therapy burdensome due to the need for daily adherence to their medication schedule. Improvements in the dosing and duration of episodic therapy have made this type of intervention more attractive than previous regimens.

Psychosocial considerations — There are also psychological aspects of recurrent genital HSV that can be distressing for some patients, which may be under-appreciated by the clinician. It is important to openly address these patient concerns and to offer counseling regarding the natural history of disease and transmission risk. In patients who experience considerable anxiety or distress, chronic suppressive therapy may be preferable, even in those with less frequent outbreaks. Patient preference should be strongly factored into these treatment decisions.

Toxicity — Antiviral therapy with acyclovir, famciclovir, or valacyclovir is extremely well tolerated during primary and episodic therapy. Although studies of chronic suppressive therapy have not shown significant toxicity, most studies have had limited long-term follow-up of one year or less [22] with few exceptions [23].

Cost of therapy — Chronic suppressive therapy is much more expensive than episodic therapy and may not be covered by all medical insurance providers.

Risk of transmission to uninfected partner — Some patients will primarily choose chronic suppressive therapy to decrease the risk of transmission of HSV to their uninfected sexual partner. Others may prefer to address this risk with consistent condom use.

Data regarding these two main strategies are discussed below.

EPISODIC TREATMENT OF RECURRENT GENITAL HERPES — Recurrent episodes of genital HSV tend to be less severe and of shorter duration.

Antiviral therapy for recurrent episodes can be dispensed either episodically to address active lesions as they occur, or continuously as suppressive therapy. The most important measures of efficacy of episodic therapy include the duration of both lesions and symptoms, as well as the proportion of aborted episodes [24]. Compared with suppressive therapy, episodic therapy is less costly and is not dependent on medication adherence to a daily regimen [24].

No study has explicitly examined the benefits versus adverse effects of antiviral therapy based upon the frequency of recurrence. The threshold level of six or more lesions per year is largely arbitrary, but is based upon the perceived
modest benefits with antiviral therapy. Patient preference is clearly an important factor in determining treatment strategy. (See ‘Suppressive therapy for recurrent genital herpes’ below.)

It is also important to realize that a number of patients may have few, if any, recurrent episodes of genital herpes. Such patients may not require antiviral therapy, particularly those with very mildly symptomatic disease or those who are not sexually active.

**Importance of timing of therapy for episodic treatment** — When used as episodic therapy, one early study demonstrated that the greatest benefit of antiviral therapy was derived by patients who self-initiated therapy compared with those who started treatment within 48 hours of lesion appearance [25]. Subsequent studies of all three antiviral agents demonstrated that early initiation of therapy (within 24 hours of symptoms) leads to faster resolution of recurrent cutaneous lesions and clinical symptoms compared with placebo [9,25]. Earlier trials generally used five days of episodic treatment, while later trials evaluated the efficacy of shorter courses of therapy (ie, one to three days) to improve patient convenience.

**Duration of therapy** — Early studies of episodic treatment utilized five days of antiviral therapy; however, subsequent studies have demonstrated that patients treated with high-dose antiviral medications for only one to three days have similar clinical benefits as those treated three times daily for the standard five-day regimen [21,24]. Brief courses of antiviral medications offer improved patient convenience.

Data on these individual agents are found below. Chronic suppression of recurrence is discussed in the next section.

**Acyclovir versus placebo** — Compared with placebo, acyclovir modestly shortens the time to crusting and healing of lesions and also decreases the duration of viral shedding [25,26]. This was shown in a study in which 131 patients with recurrent infections were randomly assigned to 800 mg of acyclovir three times daily for two days or placebo; treatment was begun within 12 hours of first signs or symptoms [26]. Compared with placebo, acyclovir was associated with more rapid healing of lesions (four versus six days) and decreased duration of viral shedding (25 versus 59 hours). Acyclovir therapy was also associated with a higher proportion of aborted clinical HSV episodes (ie, lesions never progressing past a papule).

The optimal dosing regimen for acyclovir is unclear. Similar efficacy has been reported with 800 mg three times daily for two days, 200 mg five times daily for five days, or 800 mg twice daily for five days [26,27]. However, 800 mg twice daily for five days appears to have greater efficacy in men compared with other regimens, even when initiated after the prodromal period.

**Famciclovir versus placebo** — The efficacy of famciclovir for recurrent episodes of genital HSV was illustrated in a multicenter trial of patient-initiated treatment with either famciclovir (125, 250 or 500 mg twice daily for five days) or placebo [28]. Subjects were instructed to perform cultures and to start therapy within six hours of lesion or symptom onset.

Compared with placebo, each famciclovir dose produced a significant acceleration in cutaneous healing and symptom resolution (by approximately one day) and cessation of viral shedding (by approximately two days). There was no difference with respect to lesion healing among the famciclovir dosage arms. A subsequent randomized controlled trial demonstrated that a two-day short-course regimen of famciclovir (500 mg initially, then 250 mg twice daily) was non-inferior to five days of famciclovir [24].

The efficacy of a shorter course of famciclovir (two 1000 mg doses on a single day) was evaluated for episodic treatment of genital HSV in immunocompetent patients [29]. In this multicenter, double-blind, placebo-controlled trial of 329 patients, famciclovir resulted in a faster median healing time compared with placebo (4.3 versus 6.1 days) [29]. Furthermore, the proportion of patients with aborted lesions was greater in the famciclovir group than in the placebo group (23 versus 13 percent). These preliminary data suggest that early, high-dose antiviral therapy for a brief duration of time may also be a potential therapeutic option. One-day therapy with famciclovir was also shown to be non-inferior to three days of treatment with valacyclovir [30]. (See ‘Head-to-head comparisons’ below.)

**Valacyclovir versus placebo** — Valacyclovir shortens healing time and accelerates resolution of pain by one to two days compared with untreated disease [31,32]. Three days of treatment with valacyclovir was also found to be equivalent to five days of valacyclovir in terms of healing, viral shedding, and lesion abortion [33,34].
Head-to-head comparisons — Few direct drug-to-drug comparisons have been conducted for the treatment of recurrent HSV:

- In one trial, 739 patients were randomly assigned to valacyclovir (500 mg PO twice daily) or acyclovir (200 mg PO five times daily) for five days at the time of the next recurrence [35]. There was no difference between the groups in the primary end point, which was the duration of all signs and symptoms, including lesion healing and pain and/or discomfort.

  Percentages of patients in whom all HSV cultures were negative were similar in the valacyclovir and acyclovir groups (59 and 54 percent, respectively). In patients with a positive culture before treatment, cessation of viral shedding was similarly rapid in both groups.

- In a non-inferiority study of 1179 adults with a history of recurrent genital HSV, single-day famciclovir (1000 mg twice daily) was compared with a three-day course of valacyclovir (500 mg twice daily) [30]. Mean time to healing of lesions was similar in both groups and approximately one-third of patients in each treatment arm had aborted episodes. Both regimens were well tolerated. Viral shedding was not evaluated.

Treatment recommendations for episodic therapy — We recommend individualization of treatment, after discussion of the pros and cons of therapy with each patient. Antiviral therapy may be useful for the treatment of recurrent genital lesions in patients with fewer than six episodes annually to decrease the duration of signs and symptoms associated with HSV infection and to decrease the duration of viral shedding. However, alternative strategies include no treatment or chronic suppressive therapy, as discussed above. (See ‘Treatment strategies for recurrent disease’ above.)

Although few head-to-head comparisons have been performed, all available antiviral therapies appear to be similarly efficacious. Single-day therapy is an option with famciclovir (1000 mg twice daily), which has been compared with a three-day course of valacyclovir (500 mg twice daily) with similar efficacy. If cost is a significant issue, acyclovir is generally less expensive, although it requires more frequent dosing and a longer duration of therapy. Some patients may prefer less frequent daily dosing and a longer duration of therapy, while others may prefer a shorter course of therapy.

Regardless of the antiviral agent used, treatment of recurrent episodes is associated with faster resolution of cutaneous lesions and clinical symptoms if initiated within the first 24 hours [25,26,28]. This is easiest to achieve if the patient is given a supply of medication, and therapy is initiated by the patient at the first sign of recurrence. It is important to counsel the patient that symptoms of recurrence can include tingling or paresthesias prior to the development of discrete lesions.

We agree with the 2015 Centers for Disease Control and Prevention guidelines, which recommend the following oral treatment options for episodic therapy [14]:

- Acyclovir: 800 mg three times daily for two days; or 800 mg twice daily for five days; or 400 mg three times daily for five days
- Famciclovir: 1000 mg twice daily for a single day duration; or 125 mg twice daily for five days; or 500 mg once, followed by 250 mg twice daily for two days
- Valacyclovir: 500 mg twice daily for three days or 1000 mg once daily for five days

SUPPRESSIVE THERAPY FOR RECURRENT GENITAL HERPES — Suppressive therapy for recurrent genital herpes involves the administration of daily chronic therapy, which reduces viral shedding [36]. Studies of suppressive therapy for recurrent HSV have assessed efficacy according to time to first recurrence, frequency of recurrences, severity and duration of recurrences, viral shedding, and frequency of recurrences after treatment. Of these, the most reliable clinical measures of antiviral benefit include the time to first recurrence and frequency of recurrences over time [24].

Studies have demonstrated that approximately half of patients on suppressive therapy remain recurrence-free and other patients have a significant reduction in frequency of recurrences (70 to 80 percent) [9,37]. Chronic suppressive therapy is usually offered to patients who experience six or more clinical episodes per year or who experience significant anxiety or distress related to their clinical recurrences. Suppressive therapy also decreases the risk of transmission to an uninfected sexual partner. (See ‘Valacyclovir use in discordant couples’ below.)
The safety of long-term therapy has been demonstrated over six years of continuous treatment in one study of 239 patients [23]. However, as noted above, in the natural course of disease, the number of recurrences diminishes with time, whether or not antiviral therapy is administered [38]. Thus, many experts recommend discussing the need for ongoing suppressive antiviral therapy on an annual basis [14]. However, some patients may not desire treatment discontinuation due to concerns about severity of recurrent lesions during treatment interruption, which has been reported [39].

The relative efficacy of the available antiviral medications for suppression of genital herpes has been analyzed in a large meta-analysis of 6158 immunocompetent patients from 14 randomized placebo-controlled trials [22]. Compared with placebo, suppressive antiviral therapy lowered the relative risk of developing at least one recurrence (RR of 47 percent, 95% CI of 45-49 percent). This meta-analysis demonstrated comparable efficacy of acyclovir (400 mg twice daily), valacyclovir (250 mg twice daily), famciclovir (250 mg twice daily), or once-daily valacyclovir (500 mg). Limitations of this meta-analysis include heterogeneity of dosing regimens, varying rates of follow-up, and different methods for detection of shedding. Cost and potential long-term risks of chronic therapy were not addressed.

Data on the individual agents are discussed below; most cited studies are randomized placebo-controlled trials.

**Acyclovir versus placebo** — Acyclovir has demonstrated clinical benefit in patients with frequent clinical disease (eg, six or more episodes per year) [40,41]. In the largest randomized placebo-controlled trial, four months of suppressive therapy with acyclovir (either 200 mg five times daily or 200 mg twice daily) markedly reduced the frequency of clinical recurrence and of asymptomatic viral shedding compared with placebo [40]. The median time to the first clinical recurrence was 18 days in placebo recipients, compared with over 120 days (ie, after suppression was stopped) in both acyclovir-treated groups. Another study evaluated a dosing regimen of 400 mg twice daily [18].

**Famciclovir versus placebo** — Suppressive treatment with oral famciclovir also prolongs the interval to recurrence of symptomatic episodes and decreases viral shedding [42,43]. A multicenter trial was conducted in which 375 women with a history of at least six recurrences over 12 of the previous 24 months were randomly assigned to placebo or oral famciclovir (125 mg once or twice daily, 250 mg once or twice daily, or 500 mg once daily) for a four-month period [42]. Famciclovir (250 mg twice daily) was the most effective of the regimens, prolonging the time to first recurrence (120 versus 82 days with placebo) and increasing the likelihood of remaining free of clinically confirmed genital HSV outbreaks (78 versus 42 percent). Once-daily famciclovir regimens were less effective than twice-daily regimens.

**Valacyclovir versus placebo** — Valacyclovir is also effective in reducing clinical recurrences and asymptomatic viral shedding with 500 mg dosing once daily [36,44].

In a placebo-controlled trial, 382 patients were randomly assigned to valacyclovir (500 mg daily) or placebo in a 3:1 ratio for 16 weeks [44]. After 16 weeks (day 112) with treatment, 69 percent of patients receiving valacyclovir were recurrence-free compared with only 9.5 percent of patients assigned to placebo.

In another randomized placebo-controlled trial, which was primarily designed to assess the effect of valacyclovir on transmission rates in discordant couples, those patients receiving suppressive therapy had significant treatment benefits that included:

- Fewer days of viral shedding (2.9 versus 10.8 percent of days) and fewer recurrences of genital herpes (0.11 versus 0.40 per month)
- A reduction in the incidence of clinically symptomatic genital HSV-2 infections (0.5 versus 2.2 percent per month with placebo, hazard ratio 0.25, 95% CI 0.08-0.75).

Valacyclovir was also associated with decreased rates of HSV transmission to the uninfected partner. (See “Prevention of genital herpes virus infections”, section on ‘Chronic suppressive therapy in discordant couples’.)

**Head-to-head comparison trials** — Few comparative studies have assessed the efficacy of these various agents head-to-head. Valacyclovir, famciclovir, and acyclovir appear to provide similar benefits.

**Valacyclovir versus famciclovir** — Two randomized, double-blind, placebo-controlled studies comparing famciclovir 250 mg twice daily with valacyclovir 500 mg once daily for 16 weeks demonstrated the following results [45]:

1. Fewer days of viral shedding (2.9 versus 10.8 percent of days) and fewer recurrences of genital herpes (0.11 versus 0.40 per month).
2. Increased time to the first recurrence (120 versus 82 days with placebo).
3. Increased likelihood of remaining free of clinically confirmed genital HSV outbreaks (78 versus 42 percent).
4. Once-daily famciclovir regimens were less effective than twice-daily regimens.
Valacyclovir versus acyclovir — A randomized double-blind study of valacyclovir was performed to evaluate the efficacy of valacyclovir versus placebo or acyclovir in 1479 patients with frequent recurrences [37]. Subjects were randomly assigned to receive valacyclovir (250 mg, 500 mg, or 1000 mg once daily, or 250 mg twice daily), acyclovir (400 mg twice daily), or placebo, for one year.

All subjects in the valacyclovir arms had significantly lower rates of recurrences compared with those receiving placebo. There was a dose-response relationship across all of the valacyclovir arms. Subjects assigned to twice-daily dosing of valacyclovir or acyclovir had similar rates of recurrence. A subset analysis suggested that higher doses of valacyclovir (500 mg) were more effective than lower doses in subjects with ≥10 recurrences per year.

One randomized, double-blind, crossover trial specifically addressed the issue of subclinical viral shedding with placebo compared with therapy with valacyclovir (500 mg twice daily) or acyclovir (400 mg twice daily) in 69 subjects with genital HSV-2 [46]. Subjects were instructed to collect daily genital specimens that were evaluated by culture and polymerase chain reaction. Valacyclovir and acyclovir were similarly effective; HSV was isolated in culture on 15 percent of the days while receiving placebo, compared with 0.5 percent of days on valacyclovir and 0.8 percent of days on acyclovir, a reduction of 97 percent and 95 percent, respectively.

Valacyclovir use in discordant couples — Suppressive therapy with valacyclovir is also beneficial in decreasing transmission to an uninfected sexual partner. This was demonstrated in a large randomized placebo-controlled trial of 1484 immunocompetent, heterosexual, discordant couples [36]. Partners with HSV-2 infection were randomly assigned to receive either 500 mg of valacyclovir once daily or placebo for eight months; the susceptible partner was evaluated monthly for clinical signs and symptoms of genital herpes. Suppressive therapy led to a relative reduction in overall acquisition of genital HSV-2 infection in the uninfected partner (1.9 versus 3.6 percent, hazard ratio 0.52, 95% CI 0.27-0.99). (See “Prevention of genital herpes virus infections”,.)

Treatment recommendations for suppressive therapy — Antiviral therapy effectively suppresses HSV reactivation and decreases shedding in patients with frequent recurrences. Discussions regarding long-term suppressive therapy should include disease activity, presence of psychosexual morbidity, need for drug adherence, potential toxicity of chronic therapy, and cost.

We agree with the 2015 Centers for Disease Control and Prevention guidelines, which recommend the following oral treatment options [14]:

- Acyclovir: 400 mg twice daily
- Famciclovir: 250 mg twice daily
- Valacyclovir: 500 mg once daily or 1000 mg once daily

We prefer valacyclovir 500 mg once daily for most patients. For patients with >10 recurrences annually, we use valacyclovir 1000 mg once daily [37]. One direct comparative study suggested modestly increased efficacy with valacyclovir compared with famciclovir [45]. In addition, suppressive therapy with valacyclovir has been found to decrease transmission in discordant sexual partners [36]. A more detailed discussion of suppressive therapy is found elsewhere. (See “Prevention of genital herpes virus infections”, section on ‘Chronic suppressive therapy in discordant couples’.)

Although suppressive therapy has been given for as long as six years, the use of suppressive antiviral medications should be re-evaluated periodically, since the benefits and risks beyond six years have not yet been determined [23].

CHRONIC SUPPRESSIVE THERAPY FOR DISCORDANT COUPLES — A detailed discussion of the use of chronic suppressive therapy for discordant couples is found elsewhere. (See “Prevention of genital herpes virus infections”.)

SPECIAL CONSIDERATIONS IN HIV-INFECTED PATIENTS — Immunocompromised patients with HIV may have prolonged or severe episodes of genital herpes. The initiation of antiretroviral therapy (ART) can reduce the severity
and frequency of genital lesions secondary to herpes simplex virus (HSV). However, the clinical manifestations may worsen during immune reconstitution early after initiation of ART [14].

Suppressive or episodic therapy with oral antiviral agents (acyclovir, famciclovir, or valacyclovir) can decrease the clinical manifestations of HSV among persons with HIV infection. However, the Centers for Disease Control and Prevention guidelines recommend that these agents be used at higher dosages and/or for longer durations than in HIV-uninfected patients [14].

The doses recommended for suppressive therapy are:

- **Acyclovir** 400 to 800 mg twice to three times daily
- **Famciclovir** 500 mg twice daily
- **Valacyclovir** 500 mg twice daily

The doses recommended for episodic therapy are:

- **Acyclovir** 400 mg three times daily for 5–10 days
- **Famciclovir** 500 mg twice daily for 5 to 10 days
- **Valacyclovir** 1000 mg twice daily for 5 to 10 days

Suppressive therapy should not be used to reduce HIV or HSV-2 transmission to susceptible sex partners. A more detailed discussion of the treatment of genital HSV in HIV-infected patients is found elsewhere. (See "Treatment of genital herpes simplex virus type 2 in HIV-infected patients".)

**ANTIVIRAL DRUG RESISTANCE** — The emergence of clinical infection with acyclovir-resistant HSV-2 during chronic suppressive therapy in immunocompetent patients is relatively rare [47-53]. In two large series, the rate was 0.18 and 0.32 percent, respectively [50,51]. Even when drug-resistant HSV is isolated from an immunocompetent patient, this virus, with rare exceptions, is cleared normally without adverse clinical outcome.

However, drug resistance has been observed in HIV-infected patients on long-term therapy. When acyclovir drug resistance is confirmed, cross-resistance to famciclovir and valacyclovir should be expected; foscarnet may be effective for clinical management. (See "Foscarnet: An overview").

The mechanisms of resistance to acyclovir and related compounds are discussed elsewhere. (See "Acyclovir: An overview").

**INVESTIGATIONAL AGENTS** — The use of pritelivir for the treatment of HSV-2 is under investigation. Pritelivir is an inhibitor of the HSV-2 helicase-primase complex, and acts through a mechanism that is different from that of the nucleoside analogues acyclovir, valacyclovir, and famciclovir. In a study of 156 HSV-2 positive persons with a history of genital herpes, subjects were randomly assigned to receive placebo or one of four pritelivir dosing regimens (5 mg/daily, 25 mg/daily, 75 mg/daily, 400 mg/weekly) for 28 days [54]. HSV-2 testing was done using a polymerase-chain-reaction assay on daily genital swabs. Individuals receiving the higher doses of this agent (75 mg/daily or 400 mg/weekly) had significant reductions in the rate of viral shedding and the percentage of days with genital lesions. The relative risk of viral shedding with pritelivir, compared with placebo, was 0.13 (95% CI, 0.04 to 0.38) with the 75-mg daily dose, and 0.32 (95% CI, 0.17 to 0.59) with the 400-mg weekly dose. The percentage of days with genital lesions significantly decreased in both higher dose groups (1.2 percent for both groups versus 9 percent for placebo). The two lower doses of pritelivir (5 mg/daily and 25 mg/daily) were equivalent to placebo. However, the clinical development of pritelivir was put on hold by the FDA because of unexplained toxicities in monkeys, and the future availability of this agent is uncertain.

**PATIENT COUNSELING** — The goals of counseling the patient and their sex partners is to help the patient cope with their diagnosis, prevent transmission, and identify any concerns or misconceptions. Patients need to be educated about the natural history of their infection with emphasis on viral shedding, the potential for clinical recurrence and sexual transmission even when asymptomatic.

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics
patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient information: Genital herpes (The Basics)"
- Beyond the Basics topics (see "Patient information: Genital herpes (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

- Genital herpes simplex virus infection is a common sexually transmitted disease that is found worldwide. After the primary episode, genital HSV infection can recur frequently in a subset of patients, particularly those infected with HSV-2. (See ‘Introduction’ above.)
- Over time, clinical HSV recurrences generally decrease in frequency, although there is substantial variability in the clinical course from patient to patient. Antiviral therapy does not change the biology of latent HSV, whether given during the first episode of primary infection or during recurrent disease. (See ‘Natural history of infection’ above.)
- Acyclovir, famciclovir, and valacyclovir all have similar antiviral activity against HSV, although famciclovir and valacyclovir have improved bioavailability versus acyclovir. Safety and tolerability are excellent with all three agents. (See ‘Antiviral agents’ above.)
- Among patients with a primary episode of genital HSV, we recommend antiviral therapy (Grade 1A). Clinical trials have demonstrated comparable efficacy of acyclovir, famciclovir and valacyclovir; the last has the convenience of twice-daily dosing. (See ‘Treatment of primary HSV’ above.)
- For patients with recurrent genital HSV, clinical considerations that influence the management strategy include the frequency of recurrent episodes and the severity of symptoms. Specific options include episodic therapy, chronic suppressive therapy, or no treatment.
- In a patient with ≥6 recurrent episodes per year and/or severely symptomatic disease, we suggest chronic suppressive antiviral therapy rather than episodic treatment (Grade 2B). Valacyclovir offers the convenience of once-daily therapy in this situation.
- Among patients with <6 recurrent episodes per year or moderately symptomatic disease, we suggest administration of episodic antiviral therapy rather than chronic suppression (Grade 2B). Clinical trials have demonstrated comparable efficacy of acyclovir, famciclovir, and valacyclovir. Single-day therapy with famciclovir (1000 mg twice daily) is a convenient option with similar efficacy as a three-day course of valacyclovir (500 mg twice daily). (See ‘Episodic treatment of recurrent genital herpes’ above.)
- Patient preference must also be strongly considered in choosing between these treatment strategies. The presence of severe psychological stress related to HSV outbreaks may favor suppressive therapy, regardless of frequency, whereas the lower cost and convenience of short-term therapy may favor episodic treatment for some patients. (See ‘Treatment strategies for recurrent disease’ above.)
- No therapeutic intervention may be appropriate for some patients, particularly those with infrequent episodes and/or minimal symptoms. (See ‘Therapeutic options’ above.)
- Antiviral drug resistance is rare in the immunocompetent host. (See ‘Antiviral drug resistance’ above.)
- Options for prevention of viral transmission to a HSV-seronegative partner include antiviral therapy and barrier methods. This is discussed separately. (See ‘Prevention of genital herpes virus infections’.)

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REFERENCES


