

Genital herpes and its management

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Genital herpes is an important public health disease and is the leading cause of genital ulcer disease worldwide. We present the latest evidence based guidelines from the British Association for Sexual Health and HIV (BASHH), the Centers for Disease Control and Prevention (CDC), and other expert committees to provide an up to date account of genital infection with herpes simplex virus (HSV), its clinical features and diagnosis, and a practical approach to management of affected patients. Treatment regimens have largely been based on evidence obtained from randomised controlled trials, while certain new diagnostic tests are limited by lower levels of evidence obtained only from descriptive or case studies.

Sources and selection criteria

We searched PubMed (1966-2006) for relevant studies using keywords and text terms for genital herpes. We accessed the WHO and Health Protection Agency (United Kingdom) website to assess the disease burden of genital herpes and consulted guidelines on genital herpes from the British Association for Sexual Health and HIV (2001) and the Centers for Disease Control and Prevention (CDC, 2006). Additional data and references were obtained from International Union against Sexually Transmitted Infections (IUSTI) meetings, BASHH meetings, the International Herpes Management Forum (IHMF), the World STI/HIV congress, and a personal archive of references.

Box 1 | Presentation of first episode of genital herpes

- Often severe
- Multiple grouped vesicles that rupture easily leaving painful erosions and ulcers
- In men, the lesions occur mainly on the prepuce and subpreputial areas of the penis
- In women, the lesions occur on the vulva, vagina, and cervix
- There may be associated systemic symptoms such as fever and myalgia
- Healing of uncomplicated lesions takes two to four weeks
- Severe complications are rare but can include autonomic neuropathy with urinary retention and aseptic meningitis

What causes genital herpes and how is infection acquired?

Genital herpes is caused by infection with herpes simplex virus (HSV), commonly by HSV type 2 and now increasingly by type 1. Both HSV-1 and HSV-2 infections are acquired from contact with infectious secretions on oral, genital, or anal mucosal surfaces. Genital herpes can also be acquired from contact with lesions from other anatomical sites such as the eyes and non-mucosal surfaces such as herpetic whitlow on fingers or from lesions on the buttocks and trunk.

What is the prevalence of genital herpes in the UK and worldwide?

In the UK, there was a 15% increase in the number of diagnoses of first attack of genital herpes from 16 479 cases in 1995 to 19 180 cases in 2004.¹ In the United States, an estimated 40-60 million people are infected with HSV-2, with an incidence of 1-2 million infections and 600 000-800 000 clinical cases a year.² The prevalence of genital herpes in developing countries varies from 2-74% according to the country. In some African countries that are experiencing HIV epidemics, HSV-2 is highly prevalent ($\geq 70\%$), and there is evidence that genital HSV increases the risk of HIV infection and that people with both are more likely to transmit HIV infection.³

How do patients present?

First (initial) episode of genital herpes

The initial episode is the first episode of genital infection with either HSV-1 or HSV-2 (box 1). Primary genital herpes is the first episode in an individual with no pre-existing antibodies to either HSV type. A non-primary first episode is the first infection in an individual with pre-existing antibodies to the other HSV type.^{4,5}

Recurrent genital herpes

Groups of vesicles or ulcers develop in a single anatomical site and heal within 10 days. For the first two years patients may experience an average of five clinical episodes a year, which may reduce in frequency thereafter. Genital HSV caused by type 1 infection recurs less often, and thus typing of infection may inform patient counselling.

Asymptomatic HSV infection

Most people with HSV infection have mild unrecognised or subclinical disease and are unaware of their infection. They may shed the virus intermittently in the genital tract and thus transmit the infection to their sexual partners entirely unknowingly. Subclinical shedding occurs most commonly in the first year of infection in patients with genital HSV-2 infection and in individuals with frequent symptomatic recurrences. Perianal shedding is common in HIV negative, HSV-2 seropositive men who have sex with men and are asymptomatic.^{w1} Most infections of genital herpes are transmitted by people who are unaware that they are infected or who have no symptoms when transmission occurs.

How do I make a diagnosis of genital herpes?

The clinical diagnosis of genital HSV infection has a low sensitivity and specificity; laboratory confirmation of infection and typing of HSV is essential as it influences the management, prognosis, and counselling of patients.

Detection of HSV in clinical lesions—Table 1 compares the methods of detection. Take swabs from the base of the lesion or fluid from a vesicle. For culture tests it is essential that the cold chain (4°C) is maintained and appropriate media are used. Polymerase chain reaction (PCR) is the most useful test as less meticulous handling of specimens is required.

Serology—Commercial tests that use complement fixation are not type specific. Seroconversion from a zero baseline is usually diagnostic of a primary infection. In the case of recurrent infection, an immune response from a non-zero baseline may be detected. These tests cannot distinguish between initial and recurrent infections, however, and have been replaced by sensitive tests such as enzyme linked immunosorbent assay (ELISA) and radioimmunoassay (RIA). Type specific serology tests (TSSTs), which detect glycoprotein G2 specific to HSV-2 and glycoprotein G1 specific to HSV-1 infection, are the only commercially available diagnostic tools available to identify those with asymptomatic HSV infection and can effectively distinguish the two types with high sensitivity (80-98%) and specificity ($\geq 96\%$).⁸ Case control studies have shown that there are certain clinical settings when these tests may help the diagnosis of HSV infection^{9 w2-w4} (boxes 2 and 3).

Box 2 | When type specific serology testing can be useful^{9 w2-w4}

- The patient's partner has genital herpes and patient wants to know if he or she has been infected
- The patient presents with recurrent genital or atypical ulcers and results of culture or polymerase chain reaction tests are negative
- Screening of individuals at high risk of sexually transmitted infections
- Testing of pregnant women with undiagnosed genital herpes

Box 3 | When type specific serology testing is not useful and should not be used^{9 w2-w4}

- To differentiate oral from genital HSV-1 infection
- During the 2 to 12 weeks after infection as it is not known how long after infection the test results remain positive as antibody levels "serorevert" to normal over time
- In children aged <14 years as it has a low sensitivity and specificity
- In medicolegal cases as viral culture is the ideal test for genital herpes

How do I manage patients with genital herpes?

First episode of genital herpes

General measures (evidence level IV, grade C, table 2) for treating patients with a first episode include cleaning affected areas with normal saline, giving analgesia (systemic or local, such as lidocaine gel), and treating any secondary bacterial infection.

Specific antiviral therapy

Aciclovir has a good record of safety and efficacy and is available in generic formulations. Other drugs, such as valaciclovir and famciclovir, have less frequent dosing regimens compared with aciclovir (box 4) but are more expensive. Randomised control trials have shown that all three drugs reduce the severity and duration of clinical attacks.^{10 w5} None of these drugs eradicate the infection or latent virus.

There is no evidence of benefit from courses of treatment longer than five days. BASHH guidelines, however, recommend that treatment should be continued beyond five days if new lesions continue to form, if

Table 1 | Comparison of detection methods for HSV in clinical lesions^{6 7}

	Tzanck smear	Virus culture	Antigen detection (DFA or EIA)	PCR
Sensitivity	Low	High	Low	Highest
Specificity	Low	High	High	High
Viral typing	No	Yes	No	Yes
Comments	Shows giant cells from lesions, provides presumptive evidence of infection	Ideal test. Sensitivity declines as lesions heal	Low cost and rapid	Rapid but expensive. Useful in late clinical lesions. Test of choice in examination of cerebrospinal fluid. Used for research studies

DFA=direct fluorescent antigen; EIA=enzyme immunoassay; PCR=polymerase chain reaction.

Box 4 | Recommended regimens for first episode of genital herpes (1b, A)³⁴

- Aciclovir 200 mg orally five times a day for 5-10 days or
- Aciclovir 400 mg orally three times a day for 5-10 days or
- Valaciclovir 500 mg to 1 g orally twice a day for 5-10 days or
- Famciclovir 250 mg orally three times a day for 5-10 days

symptoms and signs are severe, or if the patient also has HIV. The guidelines also state that combined oral and topical treatment is of no additional benefit. Numerous over the counter and internet based topical and oral “herbal cures” are available. There is no scientific evidence for the use of essential oils, plant extracts, zinc, and L-lysine, and they have no place in the management of genital herpes.

Our preferred treatment is aciclovir 400 mg orally three times a day for seven days because it is effective, low cost, and patients comply with treatment.

Recurrent genital herpes

Treatment of recurrent attacks includes supportive therapy, episodic antiviral therapy, or suppressive antiviral therapy. Most recurrent attacks are mild and self limiting however, and can be managed with supportive therapy only. General measures for treating patients include cleaning the affected areas with normal saline, giving analgesia (systemic or local such as lidocaine gel), and treating secondary bacterial infection.

Supportive therapy—Supportive therapy includes saline bathing, the use of analgesia, and counselling of sexual behaviour and can be instituted when recurrences are mild and self limiting.

Episodic antiviral therapy (1a, A)—Initiate episodic antiviral therapy during the prodrome or early in an attack (box 5).^{w6} Oral aciclovir, valaciclovir,¹¹ and famciclovir^{w7} reduce the severity and duration by a median of one to two days.^{w6 w8 w9} Topical antiviral therapy is less effective than systemic therapy.^{4 w10}

Randomised controlled trials have shown all these regimens to be effective. Our preferred treatment is aciclovir 400 mg orally three times a day for five days because it is effective and low cost.

Suppressive antiviral therapy (1a, A)—Meta-analyses of randomised controlled trials have shown that suppressive antiviral therapy can significantly reduce (by 70 to 80%) the number of recurrences in patients with frequently recurring (≥ 6 recurrences a year) genital herpes.^{12 w11} Box 6 shows the recommended regimen. Patients should discontinue treatment after 12 months to assess the ongoing frequency of recurrences. The timing of this should be agreed with the patient, and recurrences should be treated.

How do I manage patients with asymptomatic HSV infection?

A landmark study by Corey et al found that daily suppressive treatment with valaciclovir can reduce HSV-2 transmission among HSV-2 discordant heterosexual couples by 75% for clinical disease and reduce acquisition (measured by serology) by 48%.¹³ Other antiviral drugs may be effective but have not been investigated.¹⁴

What are the important points to discuss when counselling patients?

Counselling infected people and their sexual partners is integral to the successful management of genital

Box 5 | Recommended regimens for episodic therapy (1a, A)³⁴

- Aciclovir 200 mg orally five times a day for 5 days or
- Aciclovir 400 mg orally three times a day for 5 days or
- Aciclovir 800 mg orally twice a day for 5 days or
- Aciclovir 800 mg orally three times a day for 2 days or
- Valaciclovir 500 mg orally twice a day for 3-5 days or
- Valaciclovir 1 g orally once a day for 5 days or
- Famciclovir 125 mg orally twice a day for 5 days or
- Famciclovir 1 g orally twice a day for 1 day

Table 2 | Details of grade of recommendation and equivalent evidence level

Grades	Requirement	Equivalent evidence level
A	At least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation	Ia—evidence obtained from meta-analysis of randomised controlled trials; Ib—evidence obtained from at least one randomised controlled trial
B	Availability of well controlled clinical studies but no randomised clinical trials on topic of recommendation	Ila—evidence obtained from at least one well designed controlled study without randomisation; I Ib—evidence obtained from at least one other type of well designed quasi-experimental study; III—evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
C	Evidence obtained from expert committed reports or opinions or clinical experiences of respected authorities, or both. Indicates absence of directly applicable clinical studies of good quality	IV—evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Box 6 | Recommended regimens for suppressive therapy (1a, A)³⁴

- Aciclovir 400 mg orally twice a day or
- Valaciclovir 250 mg orally twice a day or
- Valaciclovir 500 mg once daily or
- Valaciclovir 1 g once daily or
- Famciclovir 250 mg orally twice a day

herpes.^{w12} Physicians should provide counselling to help patients cope with infection and prevent sexual and perinatal transmission.¹⁵

We have summarised the various points that physicians need to consider and discuss when counselling patients (box 7). This guide comes from personal practices and guidance from the British Association for Sexual Health and HIV (BASHH), the Centers for Disease Control and Prevention (CDC), and the International Herpes Management Forum. Educational reading material¹⁶ and access to web based literature on genital herpes should be provided as part of the counselling process.

Box 7 | Points to discuss during counselling⁵⁻¹⁶

- Information on the natural course of the disease, the potential for recurrent attacks, and the role of asymptomatic shedding in sexual transmission. Patients should be informed that asymptomatic viral shedding is more common in genital HSV-2 than HSV-1 infection and is most frequent in the first 12 months after the infection is acquired.
- Patients with a first episode of genital herpes should be told that this does not necessarily indicate recent infection and that genital symptoms may develop several years after the infection is acquired.
- Information on antiretroviral treatments available and their impact on infectivity. Episodic as well as suppressive therapy should be discussed with patients in respect to recurrent episodes of infection.
- Patients in a stable long term relationship where one partner is not infected may remain discordant for several years despite potential repeated exposure; they should be told that the risk of sexual transmission of HSV-2 can be reduced by the daily use of valaciclovir by the infected partner.
- Abstinence from sexual activity during prodromal symptoms or when lesions are present.
- Advice to inform current and new sexual partners before initiating a sexual relationship.
- Use of condoms with new or uninfected partners, particularly in the 12 months after the first attack.
- Sexual partners of infected patients should be advised that they may be infected even if they have no symptoms. Type specific serological testing should be offered to them to determine whether they are at risk of HSV acquisition.
- Asymptomatic people who test positive for HSV-2 infection on type specific serology testing should be counselled in the same way as those with symptoms and taught to recognise the clinical manifestations of infection.
- Women with a history of genital herpes or with male partners with a history of genital herpes should inform their doctors early in any pregnancy to prevent the risk of neonatal infections.
- Pregnant women who are not infected with HSV-2 should avoid sexual intercourse with their male infected partners during the third trimester. Pregnant women who are not infected with HSV-1 should also avoid genital exposure to HSV-1 during the third trimester (such as oral sex with a partner with oral herpes and vaginal intercourse with a partner with genital HSV-1 infection).

How do I manage genital herpes in a pregnant woman?

Data from the aciclovir pregnancy registry on the use of aciclovir in pregnancy does not show any increase in the number of birth defects.^{w13}

First episode of genital herpes

For women who acquire the infection in the first and second trimester treat with oral or intravenous aciclovir in standard doses and plan for vaginal delivery. For women in who vaginal delivery is planned, continuous aciclovir in the last four weeks of pregnancy will reduce the risk of clinical recurrence at term delivery by caesarean section (1b, A).¹⁷

All women presenting with the first episode of genital herpes after 34 weeks' gestation should be delivered by caesarean section. If vaginal delivery is unavoidable, treat the mother and baby with aciclovir.

Recurrent genital herpes

In women with recurrent infection caesarean section should not be performed if there are no genital lesions at the time of delivery. Daily suppressive aciclovir in the last four weeks of pregnancy might prevent recurrences of genital herpes at term and might be cost effective.^{18 w14} If genital lesions are present at the onset of labour, experts recommend delivery by caesarean section.¹⁹

What is the interaction between genital HSV-2 and HIV?

Both HSV and HIV have reached epidemic proportions in certain developing countries. Genital herpes caused by HSV-2 infection has been shown to double the risk of becoming infected with HIV through sexual transmission.²⁰ The ulcers and breaks in the genital mucosa and skin caused by HSV-2 infection facilitate entry of the HIV virus. These lesions contain large numbers of CD4 lymphocytes, which are target cells for HIV. Transmission of HIV is more likely from people who also have HSV-2,^{w15} possibly because of high titres of HIV in genital secretions during HSV-2 reactivation.^{w16}

How do I manage genital herpes in HIV positive or immunocompromised patients?

In patients with HIV or who are otherwise immunocompromised, episodes may be prolonged, more severe, and require a longer duration of antiviral treatment (box 8). A recent study found that treatment with valaciclovir at 1 g a day significantly reduced HIV RNA genital shedding as well as the plasma viral load.²¹ These data support the hypothesis that therapy

Box 8 | Recommended regimens for daily suppressive therapy in people with HIV (1b, A)⁴

- Aciclovir 400-800 mg orally two to three times a day or
- Valaciclovir 500 mg orally twice a day or
- Famciclovir 500 mg orally twice a day

SUMMARY POINTS

Genital herpes is the leading cause of genital ulcer disease worldwide

Most patients with genital herpes have no symptoms and shed virus intermittently in the genital tract

Counselling of patients and their sexual partners is critical in the management of genital herpes

Caesarean section is recommended for all pregnant women presenting with a first episode of genital herpes after 34 weeks' gestation

Genital herpes caused by HSV-2 infection has been shown to double the risk of becoming infected with HIV through sexual transmission

Suppressive antiviral therapy for genital herpes should be routinely offered to people with both HSV and HIV

for genital HSV infection in people with HIV reduces the risk of their transmitting HIV and may affect the natural progression of HIV infection. Further studies to investigate this are ongoing.

What about a vaccine?

To date the development of effective vaccines has not been promising. Difficulties arise because of the complexity of the life cycle of the virus (latency) and the current lack of understanding of the human mechanism of control of primary and recurrent disease.²² A large scale study of a gD2-AS04 vaccine is being carried out to further evaluate the protective effects in women as initial studies have shown differential effects in men and women.

Conclusions

Genital herpes is an important public health disease that can cause substantial morbidity if it is undiagnosed and untreated. Clinicians should suspect HSV infection in all patients presenting with ulcers in the genital area. Genital HSV infection increases the risk of HIV infection and people with both infections are more likely to transmit HIV to their sexual partners.

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ADDITIONAL EDUCATIONAL RESOURCES

World Health Organization (www.who.int/topics/sexually_transmitted_infections/en/)—offers factsheets and latest publications and research on genital herpes

Centres for Disease Control And Prevention (www.cdc.gov/std/Herpes/default.htm)—offers factsheets on genital herpes

Sexually Transmitted Diseases Diagnostics Initiative (www.who.int/std_diagnostics)

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Information resources for patients

International Herpes Management Forum (www.ihmf.org/Patient/PatientResources.asp)—this site offers information leaflets for patients on genital herpes; the materials have been written in collaboration with people who have genital herpes to help others with the condition. The International Herpes Alliance offers support and information to those with genital herpes, those helping to manage the disease, and national patient support groups around the world

Australian Forum (www.herpes.com.au)

Herpes Health (Canadian site) (www.herpeshealth.com)

Association Herpès Actualités (French site) (www.herpes.asso.fr)

Herpes Informatie Organisatie (Dutch site) (www.hiso.nl)

New Zealand Herpes Management Forum (www.herpes.org.nz)

British Association for Sexual Health and HIV (www.bashh.org/guidelines/2002/hsv_0601.pdf)—offers the latest UK management guidelines on genital herpes

Centers for Disease Control and Prevention (www.cdc.gov/std/Herpes/default.htm)—offers facts, statistics, treatment guidelines, and other resources on genital herpes