



Complete Summary

GUIDELINE TITLE

2007 national guideline for the management of genital herpes.

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group. 2007 national guideline for the management of genital herpes. London (UK): British Association for Sexual Health and HIV (BASHH); 2007. 26 p. [107 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of genital herpes. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

- Genital herpes infection (herpes simplex virus type 1 [HSV-1] or 2 [HSV-2] infection)
- Pregnancy
- Human immunodeficiency virus (HIV) infection

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Counseling
Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations on the management of adults with genital herpes in the United Kingdom, including pregnant women and individuals co-infected with human immunodeficiency virus (HIV)

TARGET POPULATION

Adults in the United Kingdom including pregnant women and individuals co-infected with human immunodeficiency virus (HIV)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Direct detection of herpes simplex virus (HSV) in swabs taken from the base of genital lesions
2. HSV detection by polymerase chain reaction (PCR) (preferred method) or isolation in cell culture
3. Serological testing for HSV type-specific antibodies by commercial tests or Western blot

Treatment/Management

1. First episode genital herpes
 - General advice: saline bathing, analgesia, and topical anaesthetic agents
 - Treatment with antiviral drugs: aciclovir, valaciclovir, or famciclovir
 - Management of complications, including hospitalisation and catheterisation
2. Recurrent genital herpes
 - General advice: saline bathing, Vaseline, analgesia, 5% lidocaine ointment

- Episodic and suppressive antiviral treatment with aciclovir, valaciclovir, or famciclovir
3. Prevention of transmission
 - Condom use
 - Suppression of symptomatic and asymptomatic viral shedding with acyclovir, famciclovir, or valaciclovir
 4. Counselling, patient education and support, and partner notification issues
 5. Management of herpes in pregnancy
 - Referral to a Genitourinary Physician
 - Treatment with aciclovir for first episode and daily suppressive aciclovir from 36 weeks gestation, for first and second trimester acquisition of herpes
 - Continuous aciclovir in the last 4 weeks of pregnancy for third trimester acquisition of herpes
 - Consideration of aciclovir suppressive therapy beginning at 36 weeks gestation for recurrent herpes
 - Vaginal delivery or offer of Caesarean section, as indicated
 - Intrapartum aciclovir treatment of mother during vaginal delivery and subsequently the neonate, as indicated
 - Patient education/counseling to prevent maternal acquisition of HSV in pregnancy
 6. Management of genital herpes in people with human immunodeficiency virus (HIV)
 - Treatment of immune reconstitution inflammatory syndrome (IRIS)-associated HSV with topical cidofovir
 - Treatment of first episode genital herpes with oral aciclovir, valaciclovir, or famciclovir
 - Repeat viral culture with susceptibility testing and increased dose of HSV therapy, if needed
 - Treatment of severe cases of first episode herpes with intravenous aciclovir
 - Optimization of highly active antiretroviral therapy (HAART) to reduce HSV recurrence
 - Suppressive antiviral treatment with aciclovir, famciclovir, or valaciclovir
 - Treatment of drug-resistant herpes in people with HIV with topical foscarnet cream and cidofovir gel or with intravenous foscarnet or cidofovir (administered with oral probenecid and adequate pre-hydration)

MAJOR OUTCOMES CONSIDERED

- Herpes simplex virus (HSV) detection rates
- Sensitivity and specificity of HSV tests
- Rate of healing of HSV lesions
- Severity of HSV episodes
- Rate of viral shedding (symptomatic and asymptomatic)
- HSV recurrence rate
- HSV transmission rate, including transmission from mother to neonate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

This review was updated by searching PubMed from 1999-2007 for publications in English using the search terms/Mesh headings: Diagnosis: "Herpes genitalis", "Herpes simplex diagnosis. Neonatal herpes: "Neonatal herpes", "pregnancy complications – infectious", "herpes near pregnancy" free text. A search of the Cochrane Library was also searched using the MeSH terms: "randomized controlled trials", "Genital Herpes", "herpes genitalis".

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- 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 control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The current guideline has been developed by the Herpes Simplex Advisory Panel, which is a special interest group of British Association of Sexual Health and HIV (BASHH). The Panel incorporates specialist clinicians, virologists, health advisers, nurses, clinical psychologist and a representative from the Herpes Viruses Association (a self help organisation). The Process was overseen by the Clinical Effectiveness Group of BASHH. This is the second revision of the guideline first written in 1999.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed, and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The draft guideline was placed on the British Association of Sexual Health and HIV (BASHH) website for a 3 month consultation period.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (**I-IV**) and grades of recommendation (**A-C**) are defined at the end of the "Major Recommendations" field.

Clinical Features

Symptoms

- The patient may be asymptomatic, and the disease unrecognised.
- Local symptoms consist of painful ulceration, dysuria, vaginal or urethral discharge.
- Systemic symptoms are much more common in primary than in initial or recurrent disease.
- Systemic symptoms consist of fever and myalgia.
- Rarely, systemic symptoms may be the only evidence of infection.

Signs

- Blistering and ulceration of the external genitalia (+/- cervix/rectum).
- Tender inguinal lymphadenitis, usually bilateral.
- In first episodes, lesions and lymphadenitis are usually bilateral. In recurrent disease, it is usual for lesions to affect favoured sites. They may alternate between sides but are usually unilateral for each episode. Lymphadenitis occurs in around 30%.

Complications

- Autonomic neuropathy, resulting in urinary retention
- Autoinoculation to fingers and adjacent skin e.g., on thighs
- Aseptic meningitis

Atypical Genital Herpes

- The lesions of recurrent episodes may be small, and may resemble non-specific erythema, erosions or fissures.
- In the United States, only about 20% of those patients who present to physicians with genital symptoms receive a correct diagnosis of genital herpes.

Diagnosis

For a detailed discussion of diagnostic methods for genital herpes please refer to the "Sexually Transmitted Infection Screening and Testing Guidelines" (2006 edition) produced by the Screening Guidelines Steering Committee of the British Association of Sexual Health and HIV (BASHH) Clinical Effectiveness Group. The diagnostic tests outlined below may not be available in all settings because of local facilities or cost.

Virus Detection and Characterisation

- The confirmation and characterisation of the infection and its type, by direct detection of herpes simplex virus (HSV) in genital lesions, are essential for diagnosis, prognosis, counselling, and management (**Level of Evidence IV, Grade of Recommendation C**).
- Methods should be used that directly demonstrate HSV in swabs taken from the base of the genital lesion. (**Level of Evidence 1b, Grade of Recommendation A**).
- Virus typing to differentiate between HSV-1 and HSV-2 should be obtained in all patients with newly diagnosed genital herpes (**Level of Evidence III, Grade of Recommendation B**).
- HSV isolation in cell culture is the current routine diagnostic method in the United Kingdom (UK). Virus culture is slow, labour-intensive, and expensive. Specificity is virtually 100%, but levels of virus shedding, quality of specimens, and sample storage and transport conditions influence sensitivity. Delayed sample processing and lack of specimen refrigeration after collection and during transport significantly reduce the yield of virus culture at all stages of the infection.
- HSV DNA detection by polymerase chain reaction (PCR) increases HSV detection rates by 11% to 71% compared with virus culture. PCR-based methods allow less stringent conditions for sample storage and transport than virus culture and new real-time PCR assays are rapid and highly specific. Real-time PCR is recommended as the preferred diagnostic method for genital herpes (**Level of Evidence Ib, Grade of Recommendation A**). PCR assays must be appropriately validated before clinical use and their availability should be discussed with service providers.

Serology

- Testing for HSV type-specific antibodies can be used to diagnose HSV infection. The detection of HSV-1 immunoglobulin G (IgG) or HSV-2 IgG or both, in a single serum sample represents HSV infection with HSV at some time. It is difficult to say whether the infection is recent as immunoglobulin M (IgM) detection is unreliable and avidity studies are not commonly available.

Collection of serum samples a few weeks apart can be used to show seroconversion and, hence, recent primary infection. HSV-2 antibodies are indicative of genital herpes. HSV-1 antibodies do not differentiate between genital and oropharyngeal infection.

- Many commercial tests for HSV antibodies are not type-specific and are of no value in the management of genital herpes. Assays should be used that detect antibodies against the antigenically unique glycoproteins, glycoprotein G1 (gG1) and glycoprotein G2 (gG2) (**Level of Evidence III, Grade of Recommendation B**).
- Western blot is the diagnostic gold-standard, but it is not commercially available. Several commercial assays, as well as validated in-house methods, are available which show 91% to 99% sensitivity and 92% to 98% specificity relative to Western blot in sexually active adults.
- Caution is needed in interpreting serology results because even highly sensitive and specific assays have poor predictive values in low prevalence populations (see Table 1 in the original guideline document). Local epidemiological data and patient demographic characteristics should guide testing and result interpretation (**Level of Evidence III, Grade of Recommendation B**).
- In patients with a low likelihood of genital herpes, a positive HSV-2 antibody result should be confirmed in a repeat sample or by a different assay (**Level of Evidence III, Grade of Recommendation B**).
- Type-specific immune responses usually take several weeks to develop. The median time to antibody detection may vary between different assays. False negative results may be obtained early after infection, requiring follow-up samples to demonstrate seroconversion.
- The value of routine screening of all genitourinary medicine clinic attendees or antenatal patients and their partners for HSV antibodies remains to be established. Serology may be helpful in the following situations (**Level of Evidence III, Grade of Recommendation B**):
 - Recurrent genital disease of unknown cause
 - Counselling patients with initial episodes of disease, including pregnant women
 - Investigating asymptomatic partners of patients with genital herpes, including pregnant women

Management

First Episode Genital Herpes

General Advice

- Saline bathing
- Analgesia
- Topical anaesthetic agents e.g., 5% lidocaine (lignocaine) ointment may be useful to apply especially prior to micturition but should be used with caution because of the risk of potential sensitization.

Antiviral Drugs

- Oral antiviral drugs are indicated within 5 days of the start of the episode and while new lesions are still forming.

- Aciclovir, valaciclovir, and famciclovir all reduce the severity and duration of episodes (**Level of Evidence Ib, Grade of Recommendation A**).
- Antiviral therapy does not alter the natural history of the disease.
- Topical agents are less effective than oral agents.
- Combined oral and topical treatment is of no benefit.
- Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting.
- There is no evidence for benefit from courses longer than five days. However, it may be prudent to review the patient after 5 days and continue therapy if new lesions are still appearing at this time.

Recommended Regimens (All for Five Days)

- Aciclovir 200 mg five times daily
- Aciclovir 400 mg three times daily
- Valaciclovir 500 mg twice daily
- Famciclovir 250 mg three times daily

Management of Complications

- Hospitalisation may be required for urinary retention, meningism, and severe constitutional symptoms.
- If catheterisation is required, suprapubic catheterisation is preferred to prevent theoretical risk of ascending infection, to reduce the pain associated with the procedure, to allow normal micturition to be restored without multiple removals and recatheterisations (**Level of Evidence IV, Grade of Recommendation C**)

Recurrent Genital Herpes

- Recurrences are self-limiting and generally cause minor symptoms.
- Management decisions should be made in partnership with the patient. Strategies include:
 - Supportive therapy only
 - Episodic antiviral treatments
 - Suppressive antiviral therapy
- The best strategy for managing an individual patient may change over time according to recurrence frequency, symptom severity, and relationship status.
- General advice (**Level of Evidence IV, Grade of Recommendation C**)
 - Saline bathing
 - Vaseline
 - Analgesia
 - 5% lidocaine (lignocaine) ointment

Episodic Antiviral Treatment (Level of Evidence Ia, Grade of Recommendation A)

- Oral aciclovir, valaciclovir, and famciclovir reduce the duration (by median of 1 to 2 days) and severity of recurrent genital herpes.
- Patient initiated treatment started early in an episode is most likely to be effective.
- Recommended regimens (all for five days)

- Aciclovir 200 mg five times daily
- Aciclovir 400 mg three times daily for 3 to 5 days
- Valaciclovir 500 mg twice daily
- Famciclovir 125 mg twice daily
- Short course therapies
 - Aciclovir 800 mg three times daily for 2 days
 - Famciclovir 1 g twice a day (bd) for one day
 - Valaciclovir 500 mg bd for 3 days

Suppressive Antiviral Therapy

- Patients who have taken part in trials of suppressive therapy have had at least six recurrences per annum. Such patients have fewer or no episodes on suppressive therapy (**Level of Evidence Ib, Grade of Recommendation A**). Patients with lower rates of recurrence will probably also have fewer recurrences with treatment.
- Patients should be given full information on the advantages and disadvantages of suppressive therapy. The decision to start suppressive therapy is a subjective one, balancing the frequency of recurrence with the cost and inconvenience of treatment.
- Patient safety and resistance data for long-term suppressive therapy with aciclovir now extends to over 18 years of continuous surveillance (**Level of Evidence III, Grade of Recommendation B**).
- Recommended regimens (**Level of Evidence Ib, Grade of Recommendation A**):
 - Aciclovir 400 mg twice daily
 - Aciclovir 200 mg four times daily
 - Famciclovir 250 mg twice daily
 - Valaciclovir 500 mg once daily
- If breakthrough recurrences occur on standard treatment, the daily dosage should be increased e.g., aciclovir 400 mg three times daily.
- Choice of treatment depends on patient compliance and cost (see Table 3 in the original guideline document).
- Suppressive therapy should be discontinued after a maximum of a year to reassess recurrence frequency. The minimum period of assessment should include two recurrences. Patients who continue to have unacceptably high rates of recurrence may restart treatment. (**Level of Evidence IV, Grade of Recommendation C**).
- Short courses of suppressive therapy may be helpful for some patients (**Level of Evidence IV, Grade of Recommendation C**).

Asymptomatic Viral Shedding

- Occurs in individuals with genital HSV-1 and those with genital HSV-2.
- Occurs most commonly in patients with genital HSV-2 infection in the first year after infection
 - In individuals with frequent symptomatic recurrences
 - Is an important cause of transmission
 - May be reduced by aciclovir 400 mg twice daily (**Level of Evidence 1b, Grade of Recommendation A**)

Prevention of Transmission

- Condoms may be partially effective in preventing acquisition of HSV, especially in preventing transmission from infected males to their female sex partners. The efficacy of male condoms in preventing transmission from infected females to uninfected male partners has not been demonstrated, and the efficacy of female condoms to reduce HSV transmission during intercourse has not been assessed.
- Aciclovir, famciclovir, and valaciclovir all suppress symptomatic and asymptomatic viral shedding. These drugs have been shown in clinical trials to reduce asymptomatic HSV shedding by about 80% to 90%. Although the threshold for infection from asymptomatic shedding has not been established, small studies have shown that valaciclovir appears to suppress asymptomatic shedding better than famciclovir. Aciclovir (400 mg twice daily) has been shown to suppress asymptomatic shedding at least as well as valaciclovir (1000 mg daily).
- Suppressive antiviral therapy with valaciclovir 500 mg once daily reduces the rate of acquisition of HSV-2 infection and clinically symptomatic genital herpes in serodiscordant couples. In a randomised trial involving 1,484 patients treated for 8 months, 0.5% valaciclovir recipients developed symptomatic infection compared with 2.2% of placebo recipients, and 1.6% compared with 3.2% acquired HSV-2 infection. Although valaciclovir reduced the risk of acquiring symptomatic infection by 75%, approximately 60 people needed to be treated to prevent one transmission. Other antivirals may be effective but efficacy has not been proven in clinical trials.

Counselling

- Diagnosis often causes considerable distress. Most people with recurrences adjust over time but antiviral treatment can probably reduce anxiety, assist adjustment and improve quality of life (**Level of Evidence II, Grade of Recommendation B**).
- Counselling should be as practical as possible and address particular personal situations; issues for someone in a long-term relationship are likely to be different from those for someone seeking a partner.
- Disclosure is often a difficult issue for patients but is more likely to happen in the context of an on-going relationship.
- Failure by the patient to control everyday stresses does not affect recurrences.
- For most patients one or two counselling sessions with an invitation to return in case of difficulty should be enough.
- Patients who have failed to adjust to the diagnosis after a year should be considered for more intensive counselling interventions.
- Counselling should cover:
 - Natural history
 - The use of antiviral drugs for symptom control; current uncertainties about impact on infectivity should be discussed
 - Discussion of the risks of transmission by sexual contact related to the actual situation of the patient
 - Reassurance regarding transmission by fomites and autoinoculation after the first infection is over
 - Abstinence from sexual contact during lesional recurrences or prodromes
 - Transmission may occur as a result of asymptomatic viral shedding

- Seropositive patients with unrecognised recurrences can be taught to recognise symptomatic episodes after counselling and this may prevent onward transmission
- The possible benefit of condoms in reducing transmission, emphasizing that their use cannot completely prevent transmission
- Pregnancy issues for both men and women (see below)

Patient Support

- The distressing nature of symptoms and the stigma associated with HSV infection, as with other conditions, often results in impaired patient retention of information given by clinical staff.
- The Family Planning Association (FPA) produces a range of leaflets on sexual health for the National Health Service (NHS). Their leaflet on genital herpes provides comprehensive patient information based on British Association of Sexual Health and HIV (BASHH) guidelines and be purchased or viewed as a non-printable PDF file on the [FPA Web site](#).
- Patients frequently benefit from talking to the Herpes Viruses Association helpline 0845 123 2305 - weekdays

Office phone line to order patient materials 020 7607 9661

Email: info@herpes.org.uk

Website: www.herpes.org.uk

- Another useful website for patient information is provided by the International Herpes Alliance: www.herpesalliance.org

Partner Notification

- Is an effective way of detecting individuals with unrecognised disease.
- May clarify whether a partner is infected or not (utilising type-specific antibody testing if necessary). This may help to relieve anxiety about transmission or reinforce the need to reduce the risk of transmission.
- May help with the counselling process.
- Awareness of the diagnosis in a partner or ex-partner may prevent further onward transmission.

Herpes Vaccines

There are no vaccines currently approved for prevention of genital herpes although trials are ongoing. Published studies using the HSV-2 glycoprotein-D adjuvant vaccine have shown limited efficacy in preventing clinical disease and only in women who were seronegative for both HSV-1 and HSV-2 at baseline. The guideline authors do not support the use of unauthorized or unlicensed vaccines outside of clinical trials.

Management of Herpes in Pregnancy

Guidelines for genital herpes in pregnancy are categorised into management of first episodes and recurrent episodes. Accurate clinical classification is difficult. Viral isolation and typing and the testing of paired sera (if a booking specimen is available) may be helpful. Referral to a Genitourinary Physician for advice on management of women with suspected genital herpes is recommended.

First Episode Genital Herpes

First and Second Trimester Acquisition

- First episode genital herpes has been associated with first trimester miscarriage; however, there is no conclusive evidence that it causes developmental abnormality if the pregnancy continues. The occurrence of first episode genital herpes is not considered an indication for termination of pregnancy. An anomaly scan may be considered at 20 to 22 weeks gestation where this is not routine.
- Management should be in line with the clinical condition with the use of either oral or intravenous aciclovir.
- Although aciclovir is not licensed for use in pregnancy, there is substantial clinical experience supporting its safety.
- Vaginal delivery should be anticipated (**Level of Evidence IV, Grade of Recommendation C**).
- Daily suppressive aciclovir from 36 weeks gestation may be considered for women who experience a first-episode of genital herpes in order to reduce the likelihood of HSV lesions at term, and the offer of Caesarean section (CS) delivery (**Level of Evidence 1b, Grade of Recommendation B**). There are sound arguments for using aciclovir 400 mg three times a day (tid) because of the altered pharmacokinetics of the drug in late pregnancy.

Third Trimester Acquisition (Level of Evidence IV, Grade of Recommendation C)

- CS for the prevention of neonatal herpes has not been evaluated in randomised controlled trials.
- CS should be offered to all women presenting with first-episode genital herpes lesions at the time of delivery, or within 6 weeks of the expected date of delivery or onset of labour. However CS may not be of benefit in reducing transmission for women presenting with ruptured membranes for greater than four hours. In all these cases the paediatricians should be informed (**Grade of Recommendation B**).
- Continuous aciclovir in the last 4 weeks of pregnancy reduces the risk of both clinical recurrence at term and delivery by CS (**Level of Evidence Ib, Grade of Recommendation B**).
- If vaginal delivery is unavoidable or where the mother opts for a vaginal birth, prolonged rupture of membranes should be avoided and invasive procedures should not be used. Intravenous aciclovir given intrapartum to the mother and subsequently to the neonate may be considered. The paediatricians should be informed.

Recurrent Genital Herpes (Level of Evidence III, Grade of Recommendation B)

- Antiviral treatment is rarely indicated for treatment of recurrent episodes of genital herpes during pregnancy.
- Symptomatic recurrences during the third trimester are likely to be brief; vaginal delivery is appropriate if no lesions are present at delivery.
- If there are no genital lesions at delivery, CS to prevent neonatal herpes should not be performed.
- Cultures during late gestation to predict viral shedding at term are not indicated.
- Sequential cultures during late pregnancy do not predict viral shedding at term.
- The benefits of obtaining specimens for culture at delivery to identify women who are asymptotically shedding HSV are unproven.
- Aciclovir suppressive treatment from 36 weeks gestation may be considered.
- A systematic review of five randomised clinical trials involving a total enrolment of 799 patients has shown that aciclovir prophylaxis beginning at 36 weeks gestation was effective in reducing clinical HSV recurrences at the time of delivery (OR 0.25; 95% confidence interval 0.15, 0.40, reducing CS deliveries for clinical recurrence of genital herpes (OR 0.30; 95% CI 0.13, 0.67, reducing total HSV detection at delivery (OR 0.11; 95% CI 0.04, 0.31, and asymptomatic shedding at delivery (OR 0.09; 95% CI 0.02; 0.39).
(Evidence level IA, Grade of Recommendation A)
- The use of aciclovir prophylaxis may also be cost-effective.
- Two randomized controlled trials of valaciclovir prophylaxis to prevent recurrent genital herpes at term were reported in 2006. The first involved a total of 112 enrolled patients who were HSV-2 seropositive. Valaciclovir use in comparison with placebo reduced the number of women with clinical recurrences between the time of randomization and delivery (RR 0.40, 95% CI 0.2, 0.9). However, the proportions of women with viral shedding within 7 days of delivery (10.4% vs. 12.0%) and with clinical HSV lesions at delivery (5.3% vs. 14.6%) were not statistically different. The second larger study enrolled a total of 350 women with a history of genital herpes, of whom 82% had recurrent genital herpes. The use of valaciclovir as compared with placebo was associated with a significantly reduced proportion of women requiring CS delivery (4% vs. 13%, $p = 0.009$), and with positive HSV cultures (2% vs. 9%, $p < 0.02$).

Genital Lesions at Onset of Labour (Level of Evidence III, Grade of Recommendation B)

- Caesarean section (CS) should be considered for women with recurrent genital herpes lesions at the onset of labour. Recurrent genital herpes at any other time during pregnancy is not an indication for delivery by CS. The risks of vaginal delivery for the fetus are small and must be set against risks to the mother of CS.
- Clinical diagnosis of genital herpes at the time of labour correlates relatively poorly with HSV detection from genital sites or lesions by culture or PCR and fails to identify asymptomatic women who have HSV in their genital secretions at the time of labor. Thus, the presence of genital lesions has a sensitivity for HSV detection of 37% by culture and 41% by PCR.
- For women with a history of recurrent genital herpes, who would opt for Caesarean delivery if HSV lesions were to be detected at the onset of labour, daily suppressive aciclovir given from 36 weeks gestation until delivery may

be given to reduce the likelihood of HSV lesions at term (**Grade of Recommendation A**).

Prevention of Acquisition of Infection (Level of Evidence IV, Grade of Recommendation C)

- Maternal risk of HSV acquisition in pregnancy varies geographically and local epidemiological surveillance should guide strategy for prevention.
- Women may be asked about or may volunteer at their first antenatal visit a history that they or their male partner have had genital herpes.
- Women who report a history of genital herpes can be reassured that the risk of transmission to the neonate is very small, even if genital lesions are present at delivery.
- Recurrences during pregnancy pose no threat to the pregnancy or well-being of the foetus.
- Identifying women susceptible to acquiring genital herpes in pregnancy by means of type-specific screening for HSV antibodies in pregnancy has not been shown to be cost-effective and is not currently indicated in the UK.
- Female partners of men with genital herpes, who themselves give no history of genital herpes, should be advised about reducing their risk of acquiring this infection. Women may reduce their risk of acquiring herpes during pregnancy and of subsequent transmission to the neonate by using condoms consistently, especially the third trimester, and abstaining from sexual intercourse during recurrences. Women should avoid receptive oro-genital contact if their partner has oro-labial herpes.
- All women, not just those with a history of genital herpes, should undergo careful vulval inspection at the onset of labour to look for clinical signs of Herpes simplex infection.
- Neonatal herpes may occur as a result of nosocomial or community-acquired infection. Mothers, staff, and other relatives/friends with active HSV infection, such as orolabial herpes or herpetic whitlow, should avoid direct contact between lesions and the neonate.

Management of Herpes in People with Human Immunodeficiency Virus (HIV)

- There is epidemiological synergy between HSV and HIV infections. Herpes simplex infections activate HIV replication and may facilitate onward HIV transmission to sexual partners. Suppressive treatment of HSV-2 infection with valaciclovir has been shown to reduce genital HIV shedding in women. In addition, both prevalent and incident HSV 2 infections are associated with an increased risk of HIV acquisition.
- Genital herpes is the most common sexually transmitted infection (STI) in HIV positive heterosexuals in the UK. The natural history of genital herpes in untreated people with HIV (PWHIV) is significantly different from that in HIV-negative individuals. The most important risk factor for herpes reactivation is the degree of HIV associated immunosuppression.
- Standard systemic antiviral drugs, as used to treat genital herpes in HIV-uninfected patients, have been shown to successfully treat genital herpes PWHIV. Resistance to antiherpes drugs is more common in those with HIV co-infection and is associated with treatment failure of genital herpes.

- Much of the evidence on herpes management in PWHIV comes from studies performed before the era of combination antiretroviral therapy; prospective studies performed early in the epidemic showed that clinical lesions might be persistent and progressive in those with HIV. Genital herpes, including chronic erosive lesions may occur as a manifestation of the immune reconstitution inflammatory syndrome (IRIS) following combination antiretroviral therapy. HSV associated IRIS may be unresponsive to previously effective anti-herpes viral therapy in the absence of increased antiviral resistance. Management is difficult but topical cidofovir may be effective.

First Episode Genital Herpes

- In the absence of HIV therapy, primary genital herpes may be severe and prolonged with risk of progressive, multifocal and coalescing mucocutaneous anogenital lesions. Moreover, serious and potentially life-threatening systemic complications, such as fulminant hepatitis, pneumonia, neurological disease and disseminated infection have been reported.
- Prompt initiation of therapy is recommended if herpes is suspected clinically. If new lesions are still forming after 3 to 5 days, a repeat viral culture with susceptibility testing should be performed and the dose of HSV therapy increased. Definitive studies in PWHIV are lacking.
 - Recommended regimens. (**Level of Evidence IIb, Grade of Recommendation B**)
 - Aciclovir 400 mg five times daily for 7 to 10 days
 - Valaciclovir 1 g twice daily for 10 days
 - Famciclovir 250 mg to 750 mg twice daily for 10 days
- In severe cases, initiation of therapy with aciclovir 5 mg/kg body weight to 10 mg/kg body weight intravenous every 8 hours may be necessary. Induction therapy should be continued intravenously for 2 to 7 days, or until clinical improvement, and followed by oral antiviral therapy to complete a minimum of 10 days total treatment. (**Level of Evidence IV, Grade of Recommendation C**).

Recurrent Genital Herpes

Both clinical and subclinical reactivations of genital herpes are more frequent in PWHIV and may lead to persistent and progressive anogenital mucocutaneous lesions, especially with cluster of differentiation 4 (CD4) cell counts less than 50 per cubic millimetre. Optimising the control of HIV replication with combination antiretroviral therapy is of fundamental importance for the management of recurrent genital herpes. Highly Active Retroviral Therapy (HAART) will reduce the frequency of clinical recurrences but has less effect upon asymptomatic viral shedding. Thereafter, specific antiviral drugs can be used for either episodic or suppressive treatment.

Episodic Treatment

In controlled trials in HSV and HIV co-infected persons, episodic treatment with the following regimens was found to be effective.

- Famciclovir 500 mg twice daily for 7 days was as effective as aciclovir 400 mg five times daily for 7 days (**Level of Evidence Ib, Grade of Recommendation A**).
- Valaciclovir 1 g twice daily for 5 days was no less effective than aciclovir 200 mg five times daily for 5 days (**Level of Evidence Ib, Grade of Recommendation A**).
- Valaciclovir 500 mg twice daily for 3 days was equivalent to the same regimen given for 5 days (**Level of Evidence Ib, Grade of Recommendation A**).

The following drug regimens are recommended for episodic treatment (**Level of Evidence IV, Grade of Recommendation C**):

- Aciclovir 400 mg orally three times daily for 5 to 10 days
- Famciclovir 500 mg twice daily for 5 to 10 days
- Valaciclovir 1 g twice daily for 5 to 10 days

Suppressive Treatment

The efficacy of suppressive antiviral therapy in PWHIV appears to be less than in HIV-negative people. It is recommended that intermittent cessation of suppressive antiviral therapy for genital herpes should occur, especially in those in whom there is also adequate inhibition of HIV replication and rising CD4 cell counts. In some PWHIV with less frequent outbreaks of genital herpes, episodic treatment may be substituted. In others, where the pre-treatment pattern of recurrences resumes, suppressive treatment may need to restart (**Level of Evidence IV, Grade of Recommendation C**).

Recommended drug regimens for daily suppressive treatment:

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

Drug Resistant Genital Herpes

- In prospective studies, aciclovir-resistant strains have been found in around 5% to 7% isolates from genital herpes lesions in HIV-infected persons. Aciclovir resistance is confirmed if isolates require aciclovir concentrations >1 mg/l to 3 mg/l for inhibition.
- Aciclovir resistance is most commonly related to a mutation in the gene encoding HSV thymidine kinase (TK), which is responsible for initial phosphorylation of aciclovir to its active form, resulting in TK that either has reduced affinity for aciclovir or is not synthesised. TK-deficient strains are of reduced pathogenicity in immunocompetent individuals but may cause serious local and systemic disease in severely immunocompromised individuals. They appear less likely to be associated with the development of latency; hence, subsequent clinical reactivations of genital herpes are often caused by aciclovir-sensitive isolates. Partially resistant strains may sometimes be successfully treated with high dose intravenous aciclovir and other nucleoside analogues but fully aciclovir-resistant strains are resistant to valaciclovir and ganciclovir, and the majority are resistant to famciclovir. TK-deficient strains

- are susceptible to foscarnet and cidofovir which do not depend upon TK but which inhibit viral DNA polymerase.
- Antiviral susceptibility testing for HSV is not currently available in the UK. Clinical response to antiviral therapy is used to guide decisions. Advice from a clinical virologist about appropriate drug dosages and duration may be sought when clinical resistance is suspected.
 - Both topical 1% foscarnet cream and 1% cidofovir gel have been shown to produce significant benefits in lesion healing, pain reduction and virological effect in drug resistant herpes in PWHIV. (**Level of Evidence Ib, Grade of Recommendation A**)
 - There is limited evidence to support the use of topical trifluorothymidine alone or in combination with interferon-alpha (**Level of Evidence IIb, Grade of Recommendation B**).
 - Systemic therapy with either foscarnet or cidofovir is generally preferred to treat drug resistant herpes in those with HIV. There is evidence for:
 - Foscarnet 40 mg/kg body weight intravenous every 8 hours until clinical resolution. (**Level of Evidence Ib, Grade of Recommendation A**).
 - Cidofovir 5 mg/kg body weight weekly intravenous infusion (**Level of Evidence IV**)
 - Cidofovir is administered with oral probenecid and adequate pre-hydration to reduce the risk of nephrotoxicity. It may be effective in aciclovir-resistant infections that are also resistant to foscarnet. Initial therapy at 5 mg/kg is given weekly, as an infusion over one hour, for two weeks. Systemic treatment should continue until clinical resolution is attained.
 - Alternating courses of treatment with aciclovir and cidofovir for subsequent recurrences has been advocated as a strategy that may reduce the development of cidofovir-resistant strains. The efficacy, safety, and durability of the therapeutic response of these agents have yet to be determined in prospective controlled trials.

Definitions:

Levels of Evidence

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- 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 control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis, prognosis, counselling, and management of genital herpes

- Prevention of morbidity (physical and psychological) associated with genital herpes and reduced transmission and prevalence

POTENTIAL HARMS

Topical anaesthetic agents should be used with caution because of the risk of potential sensitization.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group. 2007 national guideline for the management of genital herpes. London (UK): British Association for Sexual Health and HIV (BASHH); 2007. 26 p. [107 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2007)

GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

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GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The Herpes Simplex Advisory Panel Members: Prof. George Kinghorn (*Chair*); Dr Simon Barton; Ms Jayne Bickford; Dr David Brown; Dr Frances Cowan; Dr Jane Deayton; Dr John Green; Dr Eva Jungmann; Dr Chris Maple; Ms Marian Nicholson; Dr Nigel O'Farrell; Dr Raj Patel; Dr Anne Scoular

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Herpes Simplex Advisory Panel is a special interest group of British Association of Sexual Health and HIV (BASHH). It has received unrestricted educational grants from pharmaceutical companies. Some Panel members have participated in clinical trials supported by and/or have received travel grants to attend educational meetings and/or have acted as consultants for various pharmaceutical companies including GlaxoSmithKline (GSK), Novartis, and Aventis.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of genital herpes. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [British Association of Sexual Health and HIV Web Site](#).

AVAILABILITY OF COMPANION DOCUMENTS

Auditable outcome measures are provided in the [original guideline document](#).

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 15, 2000. The information was verified by the guideline developer on October 13, 2000. This summary was updated by ECRI on June 24, 2002. This summary was updated by ECRI Institute on June 16, 2008. The updated information was verified by the guideline developer on August 13, 2008.

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