2014 UK national guideline for the management of anogenital herpes

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Summary

These guidelines concern the management of anogenital herpes simplex virus infections in adults and give advice on diagnosis, management, and counselling of patients. This guideline replaces the 2007 BASHH herpes guidelines and includes new sections on herpes proctitis, key points to cover with patients regarding transmission and removal of advice on the management if HSV in pregnancy which now has a separate joint BASHH/RCOG guideline.

Introduction and methodology

Objectives

The overall aim of the guideline is to prevent morbidity (physical and psychological) associated with genital herpes and ultimately to reduce transmission and prevalence. For some groups, particularly those at high risk of HIV, this may have the added benefit of limiting HIV cases.

The guideline provides recommendations on the management of adults with anogenital herpes in the UK. Recommendations include diagnostic tests, management of the primary or first episode of anogenital herpes and recurrences, effectiveness of therapy, prophylaxis, and prevention of transmission between partners as well as patient-centred counselling.

Target users

This guideline has been developed primarily for adults aged 16 years and older presenting to health care professionals working in departments offering Level 3 care in STI management within the United Kingdom. However, the principles of the recommendations should be adopted across all levels; levels 1 and 2 providers may need to develop local care pathways where appropriate. Additionally the principals of the guideline would be relevant to patients of all ages presenting with sexually acquired genital herpes.

Search strategy

This review was updated by searching PubMed from 1999 to 2014 for publications in English using the search terms/Mesh headings:

Diagnosis: "Herpes genitalis", "Herpes simplex diagnosis".

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NICE accredited
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NICE has accredited the process used by BASHH to produce its European guideline for the management of anogenital herpes. Accreditation is valid for 5 years from 2015. More information on accreditation can be viewed at www.nice.org.uk/accreditation

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: ''randomised controlled trials'', ''Genital Herpes'', ''herpes genitalis''.

Recommendations

Priority was given to randomised controlled trial and systematic review evidence, and recommendations made and graded on the basis of best available evidence using the system published by the US Department of Health and Human Services Agency for Healthcare Policy and Research (AHPCR), see Appendix. Conclusions were reached by informal consensus within the writing group.

Stakeholder involvement and piloting

The current guideline has been developed by the Herpes Simplex Advisory Panel which is a special interest group of BASHH. The Panel incorporates specialist clinicians, virologists, health advisers, nurses, a clinical psychologist, and a representative from the Herpes Viruses Association (a patient support charity).

The draft guideline was placed on the BASHH website for a 2-month consultation period and has been reviewed by the BASHH Public Panel. It was piloted in a representative clinic.

The process was overseen by the Clinical Effectiveness Group of BASHH.

This is the third revision of the UK national guideline first written in 1999.

Definitions

Initial episode

First episode with either herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2). Dependent on whether the individual has had prior exposure to the other type, this is further subdivided into:

Primary infection: first infection with either HSV-1 or HSV-2 in an individual with no pre-existing antibodies to either type.
Non-primary infection: first infection with either HSV-1 or HSV-2 in an individual with pre-existing antibodies to the other type.
Recurrent episode: recurrence of clinical symptoms due to reactivation of pre-existent HSV-1 or HSV-2 infection after a period of latency.

Anogenital herpes

Aetiology

- HSV-1 (the usual cause of oro-labial herpes and now the most common cause of genital herpes in the UK) or
- HSV-2 (historically the most common cause of genital herpes in the UK, and the virus type that is more likely to cause recurrent anogenital symptoms).

Natural history

- Only one-third of individuals appear to develop symptoms at the time of acquisition of infection with HSV-2.[1] Incubation of infection from acquisition to first clinical signs and symptoms in this minority of individuals ranges from 2 days to 2 weeks.
- Infection may be primary or non-primary. Disease episodes may be initial or recurrent and symptomatic or asymptomatic. It is likely that the majority of infections are acquired subclinically.
- Prior infection with HSV-1 modifies the clinical manifestations of first infection by HSV-2, usually making symptoms less severe.[1]
- After childhood, symptomatic primary infection with HSV-1 is equally likely to be acquired in the genital area or oral areas.[2,3]
- Although primary and initial genital herpes in the UK may be caused by HSV-1 or HSV-2, the majority of infections in adults are due to HSV-1 with the probability of this over HSV-2 being greater at younger age (women <50 years, men <35years).
- Following primary infection, the virus becomes latent in local sensory ganglia, periodically reactivating to cause symptomatic lesions or asymptomatic, but infectious, viral shedding.
- The median recurrence rate for genital herpes after a symptomatic first episode is 0.34 recurrences/month (i.e. approximately four recurrences per year) for HSV-2 and is four times more frequent than the recurrence rate for HSV-1.[4] Recurrence rates decline over time in most individuals, although this pattern is variable.[5]
- The majority of individuals found to be seropositive for HSV-2 type-specific antibodies subsequently develop symptomatic lesions (once aware of the range of clinical manifestations of HSV-2).[6] In some of these individuals, the number of days when virus is shed asymptomatically exceeds the number of days of symptomatic shedding associated with lesions. Virus can be shed asymptomatically

from the external genitalia, the anorectum, the cervix, and urethra.

- In HIV-positive HSV-2 seropositive individuals, both symptomatic and asymptomatic shedding are increased, especially in those with low CD4 counts and those who are also seropositive for HSV-1.[7,8]

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 non-primary 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 or perianal region (±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% of patients.
- Recurrent outbreaks are limited to the infected dermatome.

Complications

- Superinfection of lesions with candida and streptococcal species (typically occurs in the second week of lesion progression)
- Autonomic neuropathy, resulting in urinary retention.
- Autoinoculation to fingers and adjacent skin e.g. on thighs. Autoinoculation into damaged and inflamed skin has been shown to occur in both acquisition and recurrent disease.
- Aseptic meningitis

Atypical GH

- 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 presented to physicians at a university research clinic with genital symptoms received a correct diagnosis of GH.[5] This reflects the fact that a significant proportion of infections due to herpes may present atypically.

Herpes proctitis

- HSV is a significant cause of proctitis in MSM. A retrospective review in the USA found that 16% of MSM with proctitis had HSV detected by culture methods, and that 3% had herpes in addition to another rectal STI.[9]
- An Australian study comparing pathogens causing infectious proctitis in HIV-positive and HIV-negative MSM found HSV proctitis more commonly in HIV-positive compared with HIV-negative MSM (HSV-1 was found in 14.2% HIV-positive and 6.5% HIV-negative MSM, and HSV-2 in 22% HIV-positive and 12.3% HIV-negative MSM). Only 32% of MSM with HSV-associated proctitis had visible external anal ulceration.[10]

Diagnosis

The diagnostic tests outlined below may not be available in all settings because of local facilities or cost.

Virus detection and typing

- The confirmation and typing of the infection and its type, by direct detection of HSV in genital lesions, are essential for diagnosis, prognosis, counselling, and management (IV, C).
- Methods should be used that directly demonstrate HSV in swabs taken from the base of the anogenital lesion or the rectal mucosa in the case of proctitis. MSM presenting with proctitis should have a rectal swab taken for the detection of HSV (1b, A).
- Virus typing to differentiate between HSV-1 and HSV-2 should be obtained in all patients with newly diagnosed genital herpes (III, B).
- HSV DNA detection by polymerase chain reaction (PCR) increases HSV detection rates by 11–71% compared with virus culture.[11–13] 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. Other nucleic acid amplification test (NAAT) methods have also shown similar results. NAATs are recommended as the preferred diagnostic method for genital herpes (Ib, A). In-house PCR assays must be appropriately validated before clinical use.

NAATs methods are now regarded as the test of choice. Confirmatory testing of positive PCR samples is currently not considered necessary.

- HSV culture is still used in some centres but will miss approximately 30% of PCR-positive samples (most significantly patients presenting with late or with mild recurrent disease). The specificity is nearly 100%, but is influenced by virus shedding, specimen quality, sample storage, and conditions of transport.[10–12] The yield of culture at all stages of the infection is significantly reduced by delayed processing of the sample and lack of specimen refrigeration post-collection and during transport.[12,13]

Serology

- Testing for HSV type-specific antibodies can be used to diagnose HSV infection.[12] The detection of HSV-1 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 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.[14] Many commercial tests for HSV antibodies are not type-specific and are of no value in the management of genital herpes.[15] Urine tests are inappropriate for the diagnosis of herpes. Assays should be used that detect antibodies against the antigenically unique components of glycoproteins gG1 and gG2 (III, B).[15,16]
- 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 91–99% sensitivity and 92–98% specificity relative to Western blot in sexually active adults.[16,17] For some widely available commercial assays sensitivity is very different for HSV-2 and HSV-1, and test performance may be markedly different for samples from some ethnic groups.
- Caution is needed in interpreting serology results because even highly sensitive and specific assays have poor predictive values in low prevalence populations (Table 1). Local epidemiological data and patient demographic characteristics should guide testing and result interpretation (III, B).[18]
- 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 (III, B).

Table 1. Positive predictive values for HSV-2 antibody assays.

Clinic location	Prevalence	Positive prediction value[a]
Sexually transmitted infection clinic	25%	86%
General population antenatal clinic	5%	50%

[a]For an assay with 95% sensitivity and specificity.

- Type-specific immune responses usually take several weeks to develop.[16] 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 (III, B):
  - recurrent genital disease of unknown cause
  - counselling patients with initial episodes of disease (to help identify recent or established infection in order to aid counselling), including pregnant women
  - investigating asymptomatic partners of patients with genital herpes, including women who are planning a pregnancy or are pregnant, or couples concerned about possible susceptibility to transmission in possibly discordant relationships.

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. Although the potential for sensitisation exists in the use of topical anaesthetic agents, lidocaine is a rare sensitiser and can be used safely in genital herpes in the form of gel or ointment.[19]

Antiviral drugs

- Oral antiviral drugs are indicated within 5 days of the start of the episode, while new lesions are still forming, or if systemic symptoms persist.

- Aciclovir, valaciclovir, and famciclovir all reduce the severity and duration of episodes (Ib, A).[20–22]
- Antiviral therapy does not alter the natural history of the disease in that frequency or severity of subsequent recurrences remains unaltered.[23]
- Topical agents are less effective than oral agents.
- Combining oral and topical treatment is of no additional benefit over oral treatment alone.
- Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting.
- There are no comparative studies to show benefit from therapy longer than 5 days. However, it may still be prudent to review the patient after 5 days and continue therapy if new lesions are still appearing at this time, or if systemic symptoms are still present, or if complications have occurred.

Recommended regimens (all for 5 days):

- Preferred regimens:
  - aciclovir 400 mg three times daily
  - valaciclovir 500 mg twice daily
- Alternative regimens:
  - aciclovir 200 mg five times 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, consideration should be given as to whether a suprapubic approach offers better symptom control to the individual patient.

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 (IV, C)

- Saline bathing
- Petroleum jelly (e.g. Vaseline)

- Analgesia
- 5% lidocaine (lignocaine) ointment

Episodic antiviral treatment (Ia, A)

- Oral aciclovir, valaciclovir, and famciclovir reduce the duration and severity of recurrent GH.[24–26]
- The reduction in duration is a median of 1–2 days.
- Head-to-head studies show no advantage of one therapy over another or the advantage of extended 5-day treatment over short-course therapy.
- Prodrugs (such as valaciclovir and famciclovir) offer simplified twice-a-day dosing.
- Aborted lesions have been documented in up to a third of patients with early treatment.[27]
- Patient-initiated treatment started early in an episode is most likely to be effective, as treatment prior to the development of papules is of greatest benefit.
- Short-course therapies offer more convenient and cost-effective strategies for managing GH episodically and should be regarded as first-line options

Short-course therapies

- Aciclovir 800 mg three times daily for 2 days[28]
- Famciclovir 1 g bd for 1 day[29]
- Valaciclovir 500 mg bd for 3 days[30,31]

Alternative 5-day treatment regimens

- Aciclovir 200 mg five times daily
- Aciclovir 400 mg three times daily for 3–5 days
- Valaciclovir 500 mg twice daily
- Famciclovir 125 mg twice daily

Suppressive antiviral therapy

- Patients who have taken part in trials of suppressive therapy have had to have at least six recurrences per annum. Such patients have fewer or no episodes on suppressive therapy (1b, A). Patients with lower rates of recurrence will probably also have fewer recurrences with treatment.[32,33]
- 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.
- Patients suffering from psychological morbidity for who the diagnosis causes significant anxiety may benefit from suppressive therapy.
- Patient safety and resistance data for long-term suppressive therapy with aciclovir now extends to over 20 years of continuous surveillance (III, B).[34]

This confirms that aciclovir is an extremely safe compound requiring no monitoring in previously well patients and only a dose adjustment in those with severe renal disease.

Recommended regimens (1b, A)

- Aciclovir 400 mg twice daily.
- Aciclovir 200 mg four times daily.
- Famciclovir 250 mg twice daily.[20]
- 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 (Table 2).
- Suppressive therapy should be discontinued after a maximum of a year to reassess recurrence frequency. The minimum period of assessment should include two recurrences since a recurrence often occurs when ending suppression. Patients who continue to have unacceptably high rates of recurrence or problematic disease may restart treatment. (IV, C).
- Short courses of suppressive therapy may be helpful for some patients (IV, C). Clinicians need to note that the full suppressive effect is usually only obtained 5 days into treatment.

Herpes proctitis

- In view of HSV being a common cause of proctitis in MSM, clinicians should consider empirical treatment for HSV in the presence of symptomatic proctitis. Antiviral treatment is as for genital herpes.[35]

Asymptomatic viral shedding

- Occurs in individuals with genital HSV-1 and those with genital HSV-2.

Table 2. Relative costs of antiviral drugs for treating genital herpes.[a]

Indication	Treatment duration	Aciclovir	Famciclovir	Valaciclovir
First episode	5 days	£1.43	£94.57	£15.70
Recurrence	5 days	£1.43	£30.02	£15.70
Suppression	1 year	£69.48	£4602.41	£73.87

[a]Source of costing DMG tariff BNF September 2013–March 2014. (Different prices may be negotiated by NHS hospital trusts).[106]

- Occurs most commonly in patients with genital HSV-2 in the first year after infection and in individuals with frequent symptomatic recurrences.
- Is an important cause of transmission
- Is reduced by all antiviral therapies
- For many patients it will decline with time.

Prevention of transmission

- Infected persons should be informed that male condoms, when used consistently and correctly, might reduce the risk of genital herpes transmission.[36–38] A 50% reduction in rate of transmission is seen in those using condoms for at least 25–60% of the time. The protective effect appears greater for women.[37]
- 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 80–90%. Although the threshold for infection from asymptomatic shedding has not been established, small studies have shown that valaciclovir appears to suppress asymptomatic shedding better then famciclovir.[39] Aciclovir (400 mg twice daily) has been shown to suppress asymptomatic shedding at least as well as valaciclovir (1000 mg daily).[40]
- 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.[41] Other antivirals may be effective but efficacy has not been proven in clinical trials. The valaciclvoir transmission study was conducted in monogamous HIV-negative serodiscordant heterosexual couples. Impact of suppressive therapy in preventing transmission in pregnancy, homosexuals, or those that are HIV-serodiscordant relationships should not be presumed where transmissions may occur more easily. Similar studies of HIV-positive patients show limited impact on HSV transmission suggesting that susceptibility is higher or that the levels of suppression of viral shedding is not adequate with currently available antivirals.[42–45]

HSV transmission: Key points to cover with patients

- Abstinence from sexual contact is recommended during lesion recurrences or prodromes.
- Transmission may occur as a result of asymptomatic viral shedding.
- Male condoms, when used consistently and correctly, may reduce the risk of genital herpes

transmission, although their use cannot completely prevent it.

- Suppressive antiviral therapy with antivirals reduces the rate of acquisition of symptomatic genital herpes in serodiscordant couples.
- Disclosure is advised in all relationships
- Discussions around disclosure and transmission should be documented.

Counselling

- Diagnosis often causes considerable distress.[46] Most people with recurrences adjust over time but antiviral treatment can probably reduce anxiety, assist adjustment, and improve quality of life (II, B).[47–49]
- Care must be taken in all consultations to ensure that appropriate language is used and that alarmist terms (incurable, chronic, attacks) are avoided. Efforts should be made to ensure the patient has understood the information.
- Information and 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 with a new or potential new partner.
- Disclosure is often a difficult issue for patients but is more likely to happen in the context of an ongoing relationship. The legal responsibilities and requirements for disclosure in serodiscordant relationships are currently unclear. However, it is important that the clinician raises this issue and advises the patient that disclosure is advised in all relationships since this is associated with lower transmission risks and may be a protection against legal action. Discussions around disclosure should be documented.
- 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.
- Referral to a patient support service such as the Herpes Viruses Association may be valuable to an individual patient.
- Patients who have failed to adjust to the diagnosis after a year should be considered for more intensive counselling interventions (IV, C).
- Information and 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 (sheets, towels, toilets, etc) and autoinoculation after the first infection is over. However, autoinoculation is a common problem if skin immunity is compromised as occurs in eczema, and may be the source of eye infections – usually associated with oral HSV infection.
  - Abstinence from sexual contact during lesional recurrences or prodromes.
  - Transmission may occur as a result of asymptomatic viral shedding.
  - HSV-2 seropositive patients with unrecognised recurrences can be taught to recognise symptomatic episodes after counselling and this may prevent onward transmission.[47–50]
  - The possible benefit of condoms in reducing transmission, emphasising that their use cannot completely prevent transmission.
  - The re-infection of source partners at genital or distant sites is often a concern. Animal experiments suggest that though possible the threshold for re-infection is much higher. Currently the evidence for re-infections in humans is limited although some work does suggest this is more likely than previously thought and may be greatest for those who are immunocompromised or have HSV-1.
- Partners with the infection should understand the importance of not transmitting a new infection to someone who is pregnant. Strategies for avoiding this should be explicitly stated:
  - Conscientious use of condoms during pregnancy, especially in the last trimester, as this can prevent transmission to a seronegative pregnant partner.
  - Abstaining from sex at the time of lesion recurrence and in the last 6 weeks of pregnancy can also prevent transmission to a seronegative pregnant partner.
  - If the partner has a history of oro-facial HSV, oro-genital transmission to pregnant women should be considered and strategies to avoid transmission discussed.
- Early notification of HSV infection to the midwife and obstetrics team enables discussion and early planning in order to ensure best outcomes for neonates, as per the BASHH/RCOG Management of Genital Herpes in Pregnancy guidelines 2014.[51]
- For further details please see the 2014 BASHH Herpes in Pregnancy Guidelines.[51]

Patient support

- The distressing nature of symptoms and the stigma associated with HSV infection, as with other

conditions,[52] often results in impaired patient retention of information given by clinical staff.

- See the BASHH Patient Information Leaflet produced in association with this guideline.
- 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

Partner notification

- Is an effective way of detecting individuals with unrecognised disease.[53]
- 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. We do not support the use of unauthorised or unlicensed vaccines outside of clinical trials.

Management of genital herpes in people with HIV

- There is epidemiological synergy between HSV and HIV infections.[54,55] Herpes simplex infections activate HIV replication[56–60] and may facilitate onward HIV transmission to sexual partners.[61–63] Suppressive treatment of HSV-2 infection with valaciclovir has been shown to reduce genital HIV shedding in women (not on ARVs).[64] In addition, both prevalent and incident HSV-2 infections are associated with an increased risk of HIV acquisition.[65,66]
- Genital herpes is the most common STI in HIV-positive heterosexuals in the UK.[67] 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.[68–70]
- Standard systemic antiviral drugs, as used to treat genital herpes in HIV-uninfected patients, have been shown to successfully treat genital herpes in PWHIV.[71–76] Resistance to anti-herpes drugs is more common in those with HIV co-infection and is associated with treatment failure of genital herpes.[77] Suppressive antiviral therapy with currently available agents has been shown in multiple studies to have no impact on HIV acquisition or transmission risk. HSV treatment used only to manage or reduce HIV transmission or acquisition risk cannot be recommended (1b, A).[78,79]
- 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.[80–84] 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 of 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. In patients with advanced HIV, double the standard dose of antiviral should be considered. If new lesions are still forming after 3–5 days, a repeat viral isolation should be attempted and susceptibility testing arranged if possible. The dose of HSV therapy should also be increased. Definitive studies in PWHIV are lacking.
- Recommended regimens.[22]
  ○ Aciclovir 400 mg five times daily for 7–10 days (IV, C)
  ○ Valaciclovir 500mg – 1g twice daily for 10 days (IV, C)
  ○ Famciclovir 250–500 mg three times daily for 10 days (IV, C)
- Therapy should be continued until all lesions have re-epithelialised.

- In severe cases, initiation of intravenous therapy with aciclovir 5–10 mg/kg body weight IV every 8 hours may be necessary. This should be continued intravenously for 2–7 days, or until clinical improvement, and followed by oral antiviral therapy to complete a minimum of 10 days total treatment (evidence level IV, 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 CD4 cell counts <50 cells/μL. Features can be atypical in nature and hypertrophic lesions can occur. Optimising the control of HIV replication with combination antiretroviral therapy is of fundamental importance for the management of recurrent genital herpes. 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

Duration of therapy

- It is likely that 5 days of therapy will be adequate for most patients. It should be noted that in advanced disease many patients will continue to have new lesions developing at the end of a standard 5-day course. Shorter courses of therapy may be adequate in those with higher CD4 counts (>500 cells/μL) although there is very limited trial evidence to support this approach. One trial with famciclovir has reported this effect.[85]

Dosage of antivirals

- Providing there is no evidence of immune failure standard doses of antivirals should suffice (Ib, A). In those with advanced disease it may be necessary to double the standard dose and to continue therapy beyond 5 days (Ib, B). Currently there is no evidence to support the use of ultrashort courses of episodic therapy in the immunocompromised.

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 (evidence level IV, C)
- Recommended drug regimens for daily suppressive treatment[22,86,87]
  ○ Aciclovir 400 mg orally twice to three times a day
  ○ Valaciclovir 500 mg orally twice a day
- If these options do not adequately control disease then the first option should be to double the dose. If control is still not achieved then famciclovir 500 mg orally twice a day can be tried (IIa, B).

Impact of HSV suppression on HIV progression

Detectable HIV viraemia has been shown to be reduced with suppressive antiviral therapy with aciclovir or valaciclovir.[88] This may impact on HIV progression particularly for those patients not on HAART. A large RCT in early HIV disease (CD4 counts >250 cells/μL, subjects not on HAART) showed that 400 mg bd of aciclovir suppression will sustain CD4 counts above 250 cells/μL in 16% of subjects compared to placebo. However, benefits of suppressive antivirals have not been demonstrated in the presence of effective HAART.[78,79]

Drug-resistant genital herpes

- In prospective studies, aciclovir-resistant strains have been found in around 5–7% isolates from genital herpes lesions in HIV-infected persons.[89–91] Aciclovir resistance is confirmed if isolates require aciclovir concentrations >1–3 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.[92,93] 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.[92–94] TK-deficient strains are susceptible to foscarnet and cidofovir, which do not depend upon TK but 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[95] and 1% cidofovir gel[96] have been shown to produce significant benefits in lesion healing, pain reduction, and virological effect in drug-resistant herpes in PWHIV (evidence level Ib, A).
- There is limited evidence to support the use of topical trifluorothymidine alone or in combination with interferon-alpha (evidence level IIb, B).[97,98]
- 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 IV every 8 hours until clinical resolution. (evidence level Ib, A).[99,100]
  - Cidofovir 5 mg/kg body weight weekly IV infusion (evidence level IV).[101–105]
- 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 1 hour, for 2 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 is yet to be determined in prospective-controlled trials.

Auditable outcome measures

- The percentage of cases having attempted HSV detection by PCR confirmation. Performance target 97%.
- The percentage of cases having at least one detected HSV typed. Performance target 97%.
- The percentage of cases, presenting within 5 days of the onset of first episode of genital herpes, who were offered recommended antiviral therapy. Performance target 97%.
- The percentage of cases, given a diagnosis of genital herpes, who were offered both verbal and written information about genital herpes. Performance target 97%.
- The percentage of cases, with six or more herpetic recurrences annually, who were offered recommended suppressive antiviral therapy. Performance target 97%.
- The percentage of cases, provided with suppressive antiviral therapy, for whom a clear plan of duration of treatment was recorded, and who were also reviewed in accordance with this plan. Performance target 97%.

The 97% performance standards are to allow for one case in 40 audited not having the recommended documentation owing to a random performance lapse not accounted for in a list of exceptions or exclusions, or a single data-entry error.

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Appendix: Levels and grading of evidence

Level of evidence

Ia Meta-analysis of randomised controlled trials

Ib At least one randomised controlled trial

IIa At least one well designed controlled study without randomisation

IIb At least one other type of well-designed quasi-experimental study

III Well-designed non-experimental descriptive studies

IV Expert committee reports or opinions of respected authorities

Grading of recommendation

A Evidence at level Ia or Ib

B Evidence at level IIa, IIb or III

C Evidence at level IV