European Dermatology Forum

Guideline on the Management of Gential Herpes

Developed by the IUSTI-Europe Guideline Editorial Board

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2017 European guidelines for the management of genital herpes

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Abstract

Genital herpes is one of the commonest sexually transmitted infections worldwide. Using the best available evidence, this guideline recommends strategies for diagnosis, management, and follow-up of the condition as well as for minimising transmission. Early recognition and initiation of therapy is key and may reduce the duration of illness or avoid hospitalisation with complications, including urinary retention, meningism, or severe systemic illness. The guideline covers a range of common clinical scenarios, such as recurrent genital herpes, infection during pregnancy, and co-infection with human immunodeficiency virus.

Keywords

Herpes simplex, HSV, genital herpes, Europe, treatment, antibiotic

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Principle changes made to the European guidelines for the management of genital herpes

- HSV DNA detection rather than cell culture is now the gold standard for diagnosis
- Short course therapy is now the recommended treatment for episodic therapy of recurrences
- Clearer recommended regimens for suppressive therapy, including recommendations for second-stage treatment for poorly controlled patients
- Clarification of duration of course of treatment for an initial episode of HSV in HIV-positive patients to ten days

Introduction

First infection with either herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) is termed primary infection and results in either symptomatic disease at the site of viral entry (i.e. on the face or genital area) or asymptomatic, and thus unrecognised, infection. In addition, there may be systemic symptoms, as with other acute viral illnesses. Only a third of patients who acquire genital herpes have any recognised clinical features at the time of acquisition. Following infection, the virus becomes latent in the local sensory ganglion, periodically reactivating to cause symptomatic lesions, or undergo asymptomatic, but nonetheless infectious, viral shedding. Genital herpes can be caused by either HSV-1 – the usual cause of oro-labial herpes – or by HSV-2. Infection with either virus can cause an identical initial

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illness; however, the actual clinical presentation may depend upon previous HSV-1 or HSV-2 infection, and previous sites of infection. Subsequent recurrence frequency is greater for HSV-2 than HSV-1 disease when infection involves the genital area.

Transmission risk

Risk of transmission appears to be greatest during lesional recurrences or prodrome, and patients should be advised to abstain from sexual contact during this time. Transmission can occur in the absence of lesional recurrence as a result of subclinical viral shedding. Efficacy of condoms to prevent sexual transmission has not been formally assessed; however, indirect evidence from failed vaccine trials provides strong support for their consistent usage to prevent transmission to both males and females (IIb, B).[1,2] The efficacy of condoms is easier to demonstrate in male-to-female transmissions where increasing consistent use results in lower levels of transmission.

Diagnosis

Clinical diagnosis

Although classical genital herpes can be recognised by the presence of typical papular lesions progressing to vesicle and ulcer formation, associated with local adenitis and in recurrent cases preceded by prodromal symptoms, the features in many patients can be highly variable. The majority of patients will suffer from atypical lesions where signs may be easily confused with other genital dermatoses. In all cases, but in particular for atypical cases, depending upon clinical diagnosis alone should be avoided.

Laboratory diagnosis

Virus detection.

- Laboratory confirmation is recommended in all patients with suspected genital herpes, using methods that directly demonstrate the virus in genital specimens; typically swabs should be taken from the base of the lesion (vesicles should be unroofed with a needle or scalpel blade) (Ib, A).[3] Viral detection in early disease (for both first episodes and recurrences) are much more likely to be successful. Swabbing for laboratory confirmation should not be delayed if at all possible.
- HSV typing into HSV-1 and HSV-2 is recommended in all patients with first-episode genital herpes to guide counselling and management (III, B).[1]
- As HSV shedding is intermittent, testing swabs from asymptomatic patients is not recommended for routine diagnosis since it is unlikely to yield confirmation of carrier status (Ib, A).[1]
- HSV DNA detection is now considered the gold standard for diagnosis. Compared with cell culture it is both more sensitive and specific (Ib, A)[3–8] and increases HSV detection rates in mucocutaneous swabs by 11–71% and is recommended as the preferred diagnostic method (Ib, A).[3,7,8] Real-time PCR can tolerate less stringent conditions for sample storage and transport than virus culture and allows the rapid detection and typing of HSV with a lower risk of contamination than traditional PCR assays. Cell culture may occasionally be required to determine anti-viral sensitivity and to generate enough viruses for transmission studies.
- Viral antigen detection methods such as direct immunofluorescence assay, enzyme immunoassay, and Tzanck and Papanicolaou staining are no longer recommended except in extremely limited resource settings (Ib, A).[9–11]

HSV type-specific serology. Serological testing is not routinely recommended in asymptomatic patients (IV, C) but may be useful in the following groups:[1,12–17]

- History of recurrent or atypical genital disease when direct virus detection methods have been negative (III, B). HSV-2 antibodies are supportive of diagnosis of genital herpes; HSV-1 antibodies do not differentiate between genital and oropharyngeal infection. Counselling of HSV-2 IgG negative, HSV-1 IgG positive patients should take into account that HSV-1 is an uncommon cause of recurrent genital disease.[1]
- First-episode genital herpes, where differentiating between primary and established infection guides counselling and management (III, B). At the onset of symptoms, the absence of HSV IgG against the virus type detected in the genital lesion is consistent with a primary infection.[1] Seroconversion should be demonstrated at follow-up, typically at 90 days.
- Sexual partners of patients with genital herpes, where concerns are raised about transmission. Serodiscordant couples can be counselled about strategies to reduce the risk of infection and disease (Ib, A).
- Asymptomatic pregnant women should be routinely recommended to be tested if there is a history of genital herpes in the partner (IIb, B).[18–20] HSV-1 and/or HSV-2 seronegative women should be counselled about strategies to prevent a new infection with either virus type during pregnancy.

Care must be taken in interpreting negative results since antibodies to both HSV-1 and 2 may not form or be lost with time.

Limited data suggest an increased risk of perinatal HIV transmission among HSV-2 seropositive HIV-infected women.[21,22] As evidence is not consistent, testing of HIV-positive pregnant women is not routinely recommended (IV, C).[23]

HSV serological assays should be used that detect antibodies against the antigenically unique glycoproteins gG1 and gG2.[11,24] Non-type-specific HSV antibody assays are of no value in the management of genital herpes.

Western blot is the diagnostic gold standard. It is >97% sensitive and >98% specific but is labour intensive and not commercially available.[25,26]

The sensitivities and specificities of commercially available seroassays can vary significantly across populations.[27–36] The positive predictive value (PPV) in low prevalence settings can make results uninterpretable. False negative results are more likely to occur in early infection and can be resolved by repeat testing.

HSV seroprevalence rates, the presence of risk factors for genital herpes and clinical history influence the PPV of HSV type-specific serology and should guide testing and result interpretation (III, B).[13,22–31] The specificities of ELISA tests can be improved by raising the index value for interpreting positivity and testing all intermediate specimens with an alternate confirmatory test (IIa, B).[26,27,29–31]

IgM testing is not recommended in routine clinical practice. Studies suggest that 12–30% of patients lose their HSV type-specific IgG antibodies depending on their HSV types and the test used.[37]

Management

First-episode genital herpes

Indications for therapy. First episodes of genital herpes are frequently associated with a prolonged disease course. Untreated, many patients suffer general and local complications. Therapy can be highly effective and should be instigated at the earliest opportunity and on clinical suspicion alone.

Antivirals. Patients presenting within five days of the start of the episode, or while new lesions are still forming, should be given oral antiviral drugs. Aciclovir, valaciclovir and famciclovir are all effective in reducing the severity and duration of the episode (Ib, A).[38,39] No therapy alters the natural course of genital herpes infection.

Topical agents are not recommended as they are less effective than oral agents and easily generate resistance (IV, C).[40]

The only indication for the use of intravenous therapy is when the patient is unable to swallow or tolerate oral medication because of vomiting. The recommended regimens – all for 5–10 days – are as follows:

- Aciclovir 400 mg three times a day, or
- Aciclovir 200 mg five times a day, or
- Famciclovir 250 mg three times a day, or
- Valaciclovir 500 mg two times a day

Choice should be made by individual clinicians, taking cost of therapy and likely compliance into account. A number of patients will have extended episodes beyond five days. If a decision to provide five days of therapy is made, the patient should have early review to ensure they have no further lesion development, systemic symptoms or disease complications – they all will require extended therapy.

Supportive measures. Bathing with normal saline and the use of appropriate analgesia are recommended. Although the potential for sensitisation exists in the use of topical anaesthetic agents, lignocaine/lidocaine is a rare sensitiser and can be used safely in genital herpes in the form of gel or ointment.[41] Benzocaine, however, is a potent sensitiser and should not be used (IV, C). In women with severe dysuria, urination with the genitals submerged in water or physiological saline solution along with spreading the labia can alleviate symptoms.

Counselling. It is important to be frank about transmission risks including subclinical shedding and the limited impact of condoms and antivirals. Advice on disclosure should be practical and tailored to the patient's personal situation. The low physical morbidity and high population prevalence should be stressed. Clear information about pregnancy is important both to men and women. High distress at diagnosis is common, often persists with recurrences and may be reduced by antivirals (Ib, A).[42–44] Most patients require one or two sessions but adjustment is difficult to predict and careful follow-up is important with more intensive input for those who do not adjust within 3–6 months.

Management of complications. Hospitalisation may be required for urinary retention, meningism, severe constitutional symptoms or adverse social circumstances. If catheterisation is required, consideration should be given as to whether a suprapubic approach offers better symptom control to the individual patient. Superinfection of lesions is rare but may occur during the second week. This is characterised by the recrudescence of local symptoms. Candida is most often implicated and is easily diagnosed and treated.

Genital HSV can theoretically be associated with superinfection of atopic dermatitis, relapsing eczema

herpeticum or be associated with recurrent erythema multiforme. Occasional case reports are described and the management is identical to that for these complications when arising from oral HSV-1.

Special situations – HIV-positive patients with first-episode genital herpes. There are no controlled trials on duration and dose of treatment. Some clinicians advocate a ten-day course of treatment at twice the standard dose of any of the usual agents (IV, C).

Information for patients

The following information should be discussed when counselling patients with first-episode genital herpes:

- The course of infection, including subclinical shedding
- Treatment options
- The risk of transmission and interventions that may limit or reduce the risk of transmission
- The risk of transmission to the infant at birth. The patient should be counselled to inform the obstetrician or midwife
- The possibility of partner notification and the possible source of infection
- That transmissions can occur from an asymptomatic partner some years into a monogamous relationship

Follow-up

Patients are followed up until the episode has resolved and counselling is considered complete. Further follow-up may be required to exclude other causes of genital ulceration that may be coexistent. Patients should be invited to re-attend should recurrences be problematic.

Recurrent genital herpes

Indications for therapy. Genital herpes recurrences are self-limiting and generally cause minor symptoms. The level of distress and the disruption caused to individual's sexual and social life are often independent of the frequency of symptoms. Decisions about how best to manage clinical recurrences should be made in partnership with the patient. Management strategies include supportive therapy only, episodic antiviral treatments, and suppressive antiviral therapy. The most appropriate strategy for managing an individual patient may vary over time according to recurrence frequency, symptom severity, and relationship status. For most patients, management will need to be supportive only, with simple local measures such as saline bathing or topical petroleum jelly being adequate.

Episodic antiviral treatment. Oral aciclovir, valaciclovir, and famciclovir are effective at reducing the duration and severity of recurrent genital herpes. The reduction in duration is a median of 1–2 days (Ib, A).[45–47] Head-to-head studies of their effects show no advantage of one therapy over another or the advantage of extended five-day treatment over ultrashort therapy. Prodrugs offer simplified twice-a-day dosing. Patient-initiated treatment started within 24 h is most likely to be effective. Aborted lesions have been documented in up to one-third of patients with early treatment.[48] To ensure prompt treatment, patients should be advised to carry a small quantity of drugs at all times.

Short course therapies should be tried in the first instance:

- Aciclovir 800 mg three times daily for two days, or[49]
- Famciclovir 1 g twice daily for one day, or[50]
- Valaciclovir 500 mg twice daily for three days (Ib, A).[49,51–54]

Alternative longer five-day courses include:

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

Suppressive therapy. The majority of early trials of suppressive therapy were done in patients with a recurrence rate equivalent to $\geq$6 recurrences/annum. More recently, studies have been completed in patients with much milder disease. These indicate that patients across all spectrums of disease will benefit from a reduced rate of recurrence with treatment. The frequency of recurrence at which it is worth starting suppressive therapy is a subjective issue and needs to balance the frequency of recurrence, the impact of disease on the individual, and the need to manage transmission risk against the cost and inconvenience of treatment.

All patients are highly likely to experience a substantial reduction in recurrence frequency on suppressive antiviral therapy. However, the majority of patients on such a regimen will still experience an occasional symptomatic recurrence.

Experience with suppressive antiviral therapy is most extensive with aciclovir (Ib, A).[55] Safety and resistance data for patients on long-term therapy now extends to over 18 years of continuous surveillance. There is no accumulative toxicity or organ damage in long-term use. Dose adjustments are only required in severe renal disease. Regular blood monitoring in otherwise well patients is not recommended. Although not essential, it may be prudent to regularly assess the need for continuing therapy, since patient circumstances

may alter significantly. However, even after prolonged periods of suppression, many patients do not find a significant alteration in disease frequency or severity upon discontinuation and reassessment.

Recommended regimens. The optimal total daily dose of suppressive aciclovir therapy is 800 mg. The only published clinical dose-ranging study concluded that 200 mg four times a day was marginally superior to 400 mg twice daily ($p<0.02$) (IIb, B).[56] However, ability to comply with a four times a day dosing regimen should determine prescribing decisions for individual patients. Twice-daily valaciclovir (250 mg twice daily) has been shown to be as effective as twice-daily aciclovir (400 mg twice daily). Once-daily aciclovir does not suppress genital herpes recurrences. There is some debate as to whether once-daily therapy is as effective as twice-daily therapy with valaciclovir. For those patients experiencing <10 recurrences per annum, a dose of 500 mg daily valaciclovir will be adequate; for those patients experiencing >10 recurrences/annum, 250 mg twice a day or 1 g once a day is required.[57]

No major clinically significant differences between suppressive therapy with valaciclovir (500 mg daily) and famciclovir (250 mg twice daily) have been documented (IV, C).[8] In patients with an insufficient clinical response, the daily suppressive dose of valaciclovir or famciclovir may have to be doubled (IV, C). Routine blood monitoring of standard dose therapy is not required. Occasionally a mild headache or nausea may occur with valaciclovir.

The decision to continue suppressive therapy should be reviewed at least annually. Discontinuation of therapy at this time, if the patient is willing, will allow a reassessment of recurrence frequency. A small number of patients will experience a reduction in recurrence frequency compared with pre-suppression symptomatic levels. The minimum period of assessment should include two recurrences to allow a view to be taken both on the frequency and severity. It is safe and reasonable to restart treatment in patients who continue to have significant disease (IV, C).

Short courses of suppressive therapy to prevent clinical symptoms may be helpful for some patients (e.g. for holidays, exams, etc.). Clinicians need to note that full suppressive effect is usually only obtained five days into treatment.

Recommended doses:

- Aciclovir 400 mg twice daily (for all frequencies of disease recurrence)
- Valaciclovir 500 mg daily (if fewer than 10 recurrences/annum)
- Valaciclovir 1 g daily (if more than 10 recurrences/annum)

Second-stage therapy for poorly controlled patients:

- Aciclovir 400 mg three times a day
- Valaciclovir 250 mg twice a day
- Valaciclovir 500 mg twice a day
- Aciclovir 200 mg four times a day

Viral shedding and transmission on suppressive therapy. Subclinical shedding of infectious virus occurs in most individuals with genital HSV-1 and/or HSV-2. Viral shedding is more likely to occur in patients with genital HSV-2, in the first year after infection, or in individuals with frequent symptomatic recurrences. Aciclovir, valaciclovir, and famciclovir all suppress symptomatic and asymptomatic viral shedding.

Even if it seems biologically plausible, partial suppression of viral shedding does not necessarily equate to reduced transmission. However, suppressive therapy with valaciclovir 500 mg a day (in those with ten or fewer recurrent episodes per year) significantly reduced transmission – by nearly 50% – in serodiscordant couples (Ib, A).[16] Twice-daily aciclovir 400 mg achieves similar levels of reduction in asymptomatic shedding to once-daily VACV. Suppressive antiviral therapy may be considered in addition to the use of condoms and selective sexual abstinence when transmission concerns are present.

Special situations

Management of HSV in the immunocompromised and HIV-positive patient

There is epidemiological synergy between Herpes simplex virus (HSV) and HIV infections.[58,59] Herpes simplex infections activate HIV replication and may facilitate onward HIV transmission to sexual partners.[60–67] Suppressive treatment of HSV-2 infection with valaciclovir has been shown to reduce genital HIV shedding in women (not on ARVs).[68] In addition, both prevalent and incident HSV-2 infections are associated with an increased risk of HIV acquisition.[69,70]

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.[71–73]

Standard systemic antiviral drugs, as used to treat genital herpes in HIV-uninfected patients, have been shown to successfully treat genital herpes in PWHIV.[74–79] Resistance to anti-herpes drugs is more common in those with HIV co-infection and is

associated with treatment failure of genital herpes.[80] 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).[81,82]

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.[83–87] 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.[88]

Management of initial episode HSV. There are no trial data for any antiviral in initial episode genital HSV in HIV-infected patients. The vast majority of adults with HIV have serological evidence of established HSV-1 and -2 infections making acquisition trials extremely difficult to perform.

Case studies report that acquisition of genital HSV may be associated with a prolonged and uncertain clinical course. Systemic symptoms may predominate and chronic lesions may become established if immunological clearance of the skin does not occur. 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.

In the absence of data, most authorities advise that multiples of the standard levels of treatment for first-episode HSV be used in the immunocompromised. However, for those with HIV these may not always be required particularly for those with normal CD4 cell count.

In patients with advanced HIV, double the standard dose of antiviral should be considered and if new lesions continue to form at day 3–5 a higher dose should be considered. Prompt initiation of therapy is recommended. 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.

Recommended initial doses in all HIV-positive patients[89]:

- Aciclovir 400 mg five times daily, for 7–10 days (IV,C)
- Valaciclovir 500–1000 mg twice daily, for ten days (IV,C)
- Famciclovir 250–500 mg three times daily, for ten days (IV,C)

Treatment should be given for at least ten days or until all lesions have re-epithelialised – this will often exceed the usual ten-day duration of treatment that is given to HIV-negative patients.

If fulminant disease ensues, then intravenous aciclovir be substituted at 5–10 mg/kg body weight every 8 h, for 2–7 days or until clinical improvement, and followed by oral antiviral therapy to complete a minimum of ten days total treatment (IV, C).

Management of recurrent disease. Both clinical and subclinical reactivations of genital herpes are more frequent in people with HIV and may lead to persistent and progressive anogenital mucocutaneous lesions, especially with CD4 cell count <50 per mm^3. Features can be atypical in nature, and larger, deeper, 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. Highly active antiretroviral 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. A number of trials of antiviral therapy in the immunocompromised have been reported.

Episodic therapy. It is likely that five days of therapy will be adequate for most patients. It should be noted that with advanced HIV 13–17% of patients have been reported to have new lesions developing at the end of a seven-day course of treatment. Shorter courses of therapy may be adequate in those with good CD4 cell count (>500 cells/mm^3) although only one trial with famciclovir has reported this effect (1b,B).[50]

Standard doses of antivirals should suffice in those with no evidence of immune failure (1b,A). In those with advanced disease it may be necessary to double the standard dose and to continue therapy beyond five days (1b,B). Caution should be exercised in using ultrashort courses of episodic therapy since these have not been evaluated fully in the immunocompromised.

Suppressive therapy. Suppressive antiviral therapy for HSV appears to be less effective in people with HIV

than in HIV-negative people but remains well tolerated. All three agents have been trialled. Standard suppressive doses of aciclovir are effective. Valaciclovir is more effective when given twice daily (500 mg bid) compared to once-daily dosing (1000 mg). The valaciclovir 500 mg once-daily dose has not been evaluated in the HIV-positive patient. Trial data for the efficacy of high-dose famciclovir are only available over much shorter durations.

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 count. In some PWHIV with less frequent outbreaks of genital herpes, episodic treatment may be substituted. In others, where the pretreatment pattern of recurrences resumes, suppressive treatment may need to restart (IV, C).

There is a considerable body of data on the safety of oral antivirals in the HIV-positive immunocompromised host. Two studies in the pre-HAART era looked at high-dose aciclovir (400 mg four times a day) and more recently at standard dose regimens. For valaciclovir a number of studies looked at the value of valaciclovir for the suppression of recurrent genital herpes. High-dose valaciclovir (2 g four times a day) has been studied and reported in HIV-positive people and those immunosuppressed and recovering from bone marrow transplants. Most recently a large number of studies looking at the efficacy of aciclovir and valaciclovir suppression and its impact on HIV transmission from co-infected patients have been reported. These trials indicate that use of oral aciclovir at standard dose and valaciclovir at 1 g od and 500 mg twice a day is associated with little or no adverse effect or toxicity as compared to the non-HIV-positive. High-dose valaciclovir (8 g daily) has been associated with Microangiopathic Haemolytic Uraemic syndrome.

Recommended drug regimens for daily suppressive treatment[89–91]

- 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).

HSV suppression to limit HIV progression. Suppressive antiviral therapy with aciclovir or valaciclovir has been shown to decrease the levels of HIV viraemia in those patients with detectable HIV viral loads through a mechanism not yet fully elucidated.[92] Such a strategy will impact on HIV progression, particularly for those individuals not on HAART. A large RCT in early HIV (those individuals not on HAART and with CD4 cell count above 250 cells/mm^3) has shown that standard doses of suppressive antiviral therapy (aciclovir 400 mg twice a day) will sustain CD4 cell count above 250 cells/mm^3 and this effect reduced the need for HAART at two years by 16% in the treatment group. However, benefits of suppressive antivirals have not been demonstrated in the presence of effective HAART.[81,82]

Management of recalcitrant herpes in immunocompromised individuals. Although rare in immunocompetent individuals, clinically refractory lesions due to genital HSV are a major problem in patients with severe immunodeficiency, including late-stage HIV diseases and patients with IRIS following combination antiretroviral therapy. Algorithms for treatment in such situations are shown in Figure 1. Systemic therapy with either foscarnet or cidofovir is generally preferred to treat drug-resistant herpes in those with HIV. There is evidence for alternating courses of treatment with aciclovir and cidofovir for subsequent recurrences 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.

In prospective studies, aciclovir-resistant strains have been found in around 5–7% isolates from genital herpes lesions in HIV-infected persons.[40,93,94] 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.[95,96] 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.[95–97] 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 has limited availability and therefore the clinical response to antiviral therapy is often used to guide decisions.

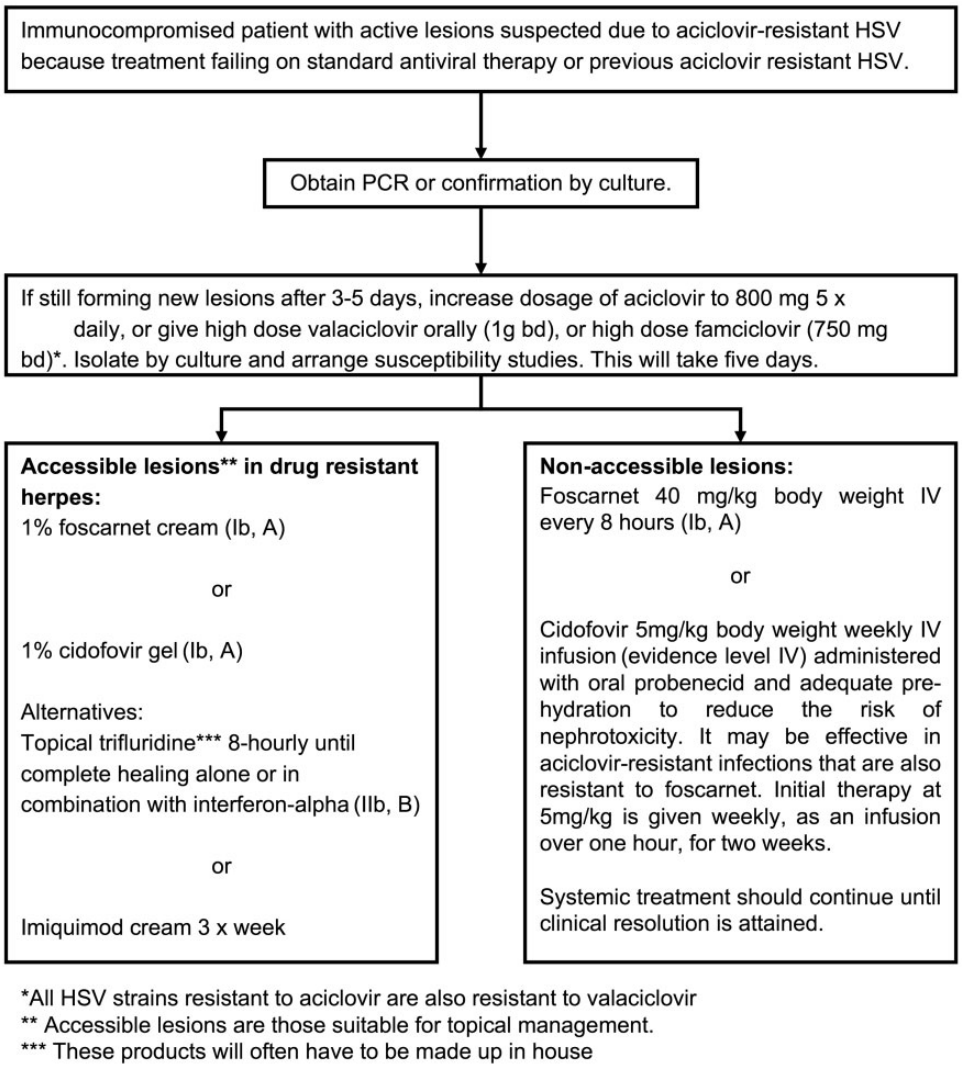

Figure 1. Algorithm for the treatment of herpes in immunocompromised individuals.

Advice from a clinical virologist about appropriate drug dosages and duration may be sought when clinical resistance is suspected.

Management of partners

There is no evidence on which to base recommendations for partner notification. On an individual basis, it may be appropriate to offer to see partners to help with the counselling process. Partner notification in relation to pregnancy is discussed below. It is worth considering the following points when counselling partners;

- The use of condoms is advisable especially when transmission concerns are present – even when the index case is on suppressive antiviral treatment.[16]
- Asymptomatic shedding plays a major role in the transmission of HSV infection and selective abstinence (abstinence during the presence of symptoms or signs) is therefore not an effective strategy for managing transmission risk.
- Partner notification is an effective way of detecting uninfected or asymptomatic individuals especially when combined with type-specific antibody testing.
- Up to 50% of asymptomatic HSV-2 seropositive women can be taught to recognise genital herpes recurrences after counselling.[98]
- Virus transmission can be reduced either with suppressive antiviral treatment or by using condoms.

Management of pregnant women with genital herpes

Management of pregnant women with first-episode genital herpes

First and second trimester acquisition. Management of the woman should be in line with her clinical

condition and will often involve the use of either oral or intravenous aciclovir in standard doses.

Providing that delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated (IV, C).

Daily suppressive aciclovir 400 mg three times a day from 36 weeks gestation may prevent HSV lesions at term and hence the need for delivery by Caesarean section (Ib, B).[99–104]

Third trimester acquisition (IV, C). Caesarean section should be considered for all women, particularly those developing symptoms within six weeks of delivery, as the risk of viral shedding in labour is very high (Ib, B).

Daily suppressive aciclovir 400 mg three times a day to delivery should be considered.

If vaginal delivery is unavoidable, prolonged rupture of membranes and invasive procedures, including the use of scalp electrodes, should be avoided. Intrapartum IV aciclovir given to the mother and subsequently to the baby may be considered and the paediatrician should be informed.[105]

Management of pregnant women with recurrent genital herpes (III, B). Women with recurrent genital herpes should be informed that the risk of neonatal herpes is low.

Management of recurrent HSV in late pregnancy. Symptomatic recurrences of genital herpes during the third trimester will be brief; vaginal delivery is appropriate if no lesions are present at delivery.

For women with a history of recurrent genital herpes who would opt for a Caesarean section if they had HSV lesions at the onset of labour, daily suppressive aciclovir 400 mg three times a day from 36 weeks gestation may prevent HSV lesions at term and hence the need for delivery by Caesarean section (Ia, A).[106]

If there are no genital lesions at delivery, there is no indication for a Caesarean section to prevent neonatal herpes.

Sequential cultures or PCR during late gestation to predict viral shedding at term are not indicated.[107]

The utility of taking cultures or PCR at delivery, in order to identify women who are asymptomatically shedding HSV, is unproven.

Management of recurrent HSV in early pregnancy. Although the safety of aciclovir in the first and second trimester of pregnancy is not fully established judicious use of this agent for suspected acquisition episodes is widely advocated. The same cannot be said for recurrent disease. Continuous or episodic therapy is not recommended in early pregnancy and should be avoided. Clinicians are on occasion obliged to use therapy for severe and complicated disease and a case-by-case assessment should be made. Newer antivirals should be avoided and the dose of aciclovir titrated down to the minimum effective level.

Management of HIV-positive women with recurrent HSV infection (IV, C). There is some evidence that HIV antibody positive women with genital HSV ulceration in pregnancy are more likely to transmit HIV infection independent of other factors.[21,23] However, this is not a consistent finding across all studies.[23]

Women who are HIV antibody positive and have a history of genital herpes should be offered daily suppressive aciclovir 400 mg three times a day from 32 weeks' gestation to reduce the risk of transmission of HIV-1 infection especially in women where a vaginal delivery is planned. Starting therapy at an earlier gestation than usual should be considered in view of the increased possibility of preterm labour (IV, C).

There is currently no evidence to recommend daily suppressive treatment for HIV-1 antibody positive women who are HSV 1 or 2 seropositive but have no history of genital herpes.

Management of women with genital lesions at onset of labour. Caesarean section may be considered for women with recurrent genital herpes lesions at the onset of labour but the risk of neonatal herpes following vaginal delivery is small and must be set against risks to the mother of Caesarean section. Evidence from the Netherlands shows that a conservative approach, allowing vaginal delivery in the presence of a recurrent anogenital lesion, was not initially associated with a rise in numbers of neonatal HSV cases (III, B).[108–110] However, this approach can only be adopted if fully supported by obstetricians and neonatologists, and if consistent with local medico-legal advice.

Clinical diagnosis of genital herpes at the time of labour correlates relatively poorly with HSV detection from genital sites by either culture or PCR and fails to identify women with asymptomatic HSV shedding.

Note: None of the antiviral drugs is licensed for use in pregnancy but the use of aciclovir in pregnancy has not been associated with any consistent pregnancy or foetal/neonatal adverse effects other than transient neutropenia.[109,111] Safety data for aciclovir may be extrapolated to valaciclovir in late pregnancy, as it is the valine ester, but there is less experience with use of valaciclovir.[112] Famciclovir should currently be avoided.

Prevention of acquisition of infection (IV, C). Maternal risk of HSV acquisition in pregnancy varies geographically and local epidemiological surveillance should guide strategy for prevention. Any strategy for prevention of neonatal herpes needs to involve both parents.

All women should be asked at their first antenatal visit if they or their partner have had genital or oral herpes.

Female partners of men with genital herpes, but without a personal history of genital herpes should be advised about reducing their risk of acquiring herpes in pregnancy and of subsequent transmission to their baby. Strategies include selective and complete abstinence (especially in the third trimester) and conscientious condom use.

Daily suppressive treatment has been shown to significantly reduce the risk of transmission of HSV to a seronegative partner; however, the effectiveness of suppressive treatment of the male partner to reduce transmission to a pregnant woman has not been evaluated so can currently only be recommended with caveats.

Pregnant women should be advised of the risk of acquiring HSV-1 as a result of receptive orogenital contact especially in the last trimester of pregnancy.

Identifying susceptible women by means of type-specific antibody testing has not been shown to be cost effective and is not indicated in Europe unless the history suggests they may be in a discordant relationship.

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 infection.

Mothers, staff, and other relatives/friends with active oral HSV lesions or herpetic whitlow should be advised to avoid direct contact between lesions and the neonate.

Management of the neonate

Babies born to mothers with first-episode genital herpes at the onset of labour. The paediatrician should be informed.

HSV PCR of urine and stool, from the oropharynx, eyes, and surface sites, should be taken to allow early identification of infected babies.

The potential benefits and risks of starting intravenous aciclovir without waiting for the results of these cultures should be discussed.

If aciclovir is not started immediately the neonate should be closely monitored for signs of lethargy, fever, poor feeding, or lesions.

Babies born to mothers with recurrent genital herpes at the onset of labour. Although some clinicians feel that taking a set of specimens for viral PCR collected 24–48 h after delivery may help with early identification of infection there is no evidence to support this practice. However, health care workers and parents should be advised to consider HSV in the differential diagnosis if the baby shows any signs of infection or develops skin, eye, or mucous membrane lesions, particularly in the first two weeks of life.

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Appendix

Search strategy

A literature search was performed using PubMed/MEDLINE, Google, The Cochrane Library and relevant guidelines from January 1981 to October 2016. A MEDLINE/PubMed search was carried out from January 1981 to October 2016 using the following search terms/Medical Subject Headings (MeSH): "HSV OR herpes", "genital ulcer OR genital ulcers" and "pregnancy complications: infectious". The search was limited to humans and the English language. For some specific recommendations, an additional MEDLINE/PubMed search was performed when necessary. A Google search was performed in October 2016 with the search term "HSV guideline OR HSV guidelines" and all relevant documents of the first 150 search results were reviewed. A search of The Cochrane Library included the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials. The following guidelines were reviewed in detail: 2010 European guideline for the management of genital herpes, 2014 BASHH guidance on the management of genital herpes, USA Centers for Disease Control and Prevention 2015 STD Treatment Guidelines, 2014 BASHH/RCOG Joint Guideline on the management of genital herpes in pregnancy, and the 2016 WHO guidelines on the treatment of genital herpes simplex viruses. The members of the guideline development group selected studies relevant to the scope of the guideline. Article titles and abstracts were reviewed and if relevant the full-text article obtained. Priority was given to randomised controlled trial and systematic review evidence and, where possible, recommendations were made and graded on the basis of the best available evidence. In areas where evidence is lacking, recommendations based on consensus opinion within the writing group have been made.

Grading of evidence

For details of the tables of levels of evidence and grading of recommendations please see: http://www.iusti.org/regions/Europe/pdf/2013/Levels_of_Evidence.pdf.

Conflicts of interests

The Work Under Consideration for Publication 2017 European guidelines for the management of genital herpes					
		Harald Moi	**Willem I. van der Meijden**	**Stephan Lautenschlager**	**Mikhail Gomberg**
1	Grant	No	No	No	No
2	Consulting fee or honorarium	No	No	No	No
3	Support for travel to meetings for the study or other purposes	No	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	No	No

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	No	No	No
2	Consultancy	No	No	No	No
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	No	No	No
6	Payment for lectures including service on speakers bureaus	No	No	No	No
7	Payment for manuscript preparation	No	No	No	No

8	Patents (planned, pending or issued)	No	No	No	No
9	Royalties	No	No	No	No
10	Payment for development of educational presentations	No	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	No	No
13	Other (err on the side of full disclosure)	No	No	No	No

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	No

Conflicts of interests

The Work Under Consideration for Publication 2017 European guidelines for the management of genital herpes					
		Harald Moi	**Elizabeth Foley**	**Rajul Patel**	**Oliver Kennedey**
1	Grant	No	no	No	No
2	Consulting fee or honorarium	No	no	No	No
3	Support for travel to meetings for the study or other purposes	No	no	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	no	DSMB for GSK and for CLJI	No
5	Payment for writing or reviewing the manuscript	No	no	no	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	no	no	No
7	Other	No	no	no	No

* This means money that your institution received for your efforts on this study.no

no

Relevant financial activities outside the submitted work					
1	Board membership	No	no	Yes (advisory Boards for GSK and BD and Roche)	No
2	Consultancy	No	no	no	No
3	Employment	No	no	no	No
4	Expert testimony	No	no	no	No
5	Grants/grants pending	No	no	no	No
6	Payment for lectures including service on speakers bureaus	No	ViiV	Roche, bd,	No

			healthcare janssen	Novartis, GSK	
7	Payment for manuscript preparation	No	no	no	No
8	Patents (planned, pending or issued)	No	no	No	No
9	Royalties	No	no	No	No
10	Payment for development of educational presentations	No	no	No	No
11	Stock/stock options	No	no	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	no	No	No
13	Other (err on the side of full disclosure)	No	no	no	No

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	no	no	No

Conflicts of interests

The Work Under Consideration for Publication 2017 European guidelines for the management of genital herpes					
		Harald Moi	**Emily Clarke**	**Gilbert Donders**	**John Green**
1	Grant	No	No	No	No
2	Consulting fee or honorarium	No	No	No	No
3	Support for travel to meetings for the study or other purposes	No	Support from Gilead to attend BHIVA 2016	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	no	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	no	No	No

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	No	Bayer Belgium	No
2	Consultancy	No	No	Medinova Switzerland	No
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	No	No	No
6	Payment for lectures including service on speakers bureaus	No	No	No	No
7	Payment for manuscript preparation	No	No	No	No

8	Patents (planned, pending or issued)	No	No	No	No
9	Royalties	No	no	No	No
10	Payment for development of educational presentations	No	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	No	No
13	Other (err on the side of full disclosure)	No	no	No	No

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	no	No	No