

2010 European guideline for the management of genital herpes

Authors: Rajul Patel¹, Steven Alderson², Anna Geretti³, Arvid Nilsen⁴, Elizabeth Foley¹, Stephan Lautenschlager⁵, John Green⁶, Willem van der Meijden⁷, Mikhail Gomberg⁸, Harald Moi⁹

¹Department of Genitourinary Medicine, Southampton, UK

²Southampton Medical School, Southampton, UK

³Department of Virology, University College London, London, UK

⁴Department of Dermatovenereology, University of Bergen, Bergen, Norway

⁵Dermatologisches Ambulatorium Triemli, Zurich, Switzerland

⁶Central and North West London NHS Trust, London, UK

⁷Department of Dermatology, Erasmus Medical Centre, Rotterdam, The Netherlands

⁸Department of Dermatology and Venereology, Moscow State University for Medicine and Dentistry, Moscow, Russia

⁹Department of Venereology, University of Oslo, Oslo, Norway

Guideline editor: Professor Harald Moi

Acknowledgements: Simon Barton, George Kinghorn, Helen Lotery

Proposed guideline review date: May 2013

IUSTI / WHO European STD guidelines Editorial Board

Keith Radcliffe (Editor-in-Chief), Marita van de Laar, Michel Janier, Jorgen Skov Jensen, Martino Neumann, Raj Patel, Jonathan Ross, Willem, van der Meijden, Pieter van Voorst Vader, Harald Moi

Search Strategy

Evidence for this guideline was provided by review of the Medline/Pubmed, Embase, Google, Cochrane Library, and relevant guidelines up to September 2008. A Medline/Pubmed and Embase search was carried out from January 1981 to September 2008, looking for the following terms in the title or abstract: »HSV/herpes«, »genital ulcers«, »HSV/herpes pregnancy«, »neonatal HSV/herpes«, and »HSV/herpes drugs«. For some specific recommendations additional Medline/Pubmed search was performed when necessary. Google search was performed in September 2007 with the search term »HSV guideline(s)« and all relevant documents of the first 150 search results were reviewed. A search of the Cochrane Library included Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Cochrane Central Register of Controlled Trials. The 2001 European Guideline for the Management of Genital Herpes was the main source for the present guideline. In addition, the following guidelines were reviewed in detail: 2006 US Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease Guidelines and 2007 British Association for Sexual Health and HIV (BASHH) National Guideline for the Management of Genital Herpes.

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. 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 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 sub-clinical 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 (IIb, B).^{1,2}

DIAGNOSIS

	Nucleic acid amplification (e.g. PCR)	Virus culture	Antigen detection (e.g. EIA)	Antigen detection (immunofluorescence on smears)
Source	Swabs	Swabs/scraping	Swabs	Smear/tissue section
Sensitivity	Highest	High, >90% from some lesions	80%	Low
Specificity	High. Containment of potential cross-contamination important	High	High	High
Advantages	High sensitivity. Allows virus detection and typing in the same test. Rapid. Automated. Labour efficient	Allows virus typing and antiviral sensitivity testing by routine methodologies	Reagent cost and speed	Inexpensive
Disadvantages	Unable to test for resistance using routine methodologies. May be expensive depending on testing methodology.	Less sensitive than PCR. Sample storage and transport conditions influence sensitivity, labour-intensive, expensive	Less sensitive than PCR. No viral typing	Insensitive. No viral typing.

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 atypical cases, depending upon clinical diagnosis alone should be avoided, whenever possible.

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 taken from the base of the lesion (vesicles should be unroofed with a needle or scalpel blade) and placed in viral transport medium (Ib, A).³

- 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
- Virus isolation in cell culture has long been regarded as the diagnostic gold standard. Advantages include high specificity and recovery of virus isolates that can be typed into HSV-1 and HSV-2 and tested for antiviral susceptibility. However, virus culture is slow (7-10 days for a negative result), labour-intensive, and poorly sensitive.⁴ Levels of virus shedding (e.g., in first vs. recurrent episodes and in early vs. late presentations) significantly influence sensitivity. Delayed sample processing and lack of refrigeration after collection significantly reduce diagnostic yield.^{5,6}
- HSV DNA detection by real-time PCR increases HSV detection rates in muco-cutaneous swabs by 11-71% compared with virus culture 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.
- Viral antigen can be detected by direct immunofluorescence assay (IFA) using fluorescein-labelled monoclonal antibodies on smears, or by enzyme immunoassay (EIA) on swabs. These assays are 10-100 fold less sensitive than virus culture and are not generally recommended (Ib, A).^{9,10,11} As EIA performs satisfactorily in symptomatic patients, it may offer a rapid diagnostic alternative in settings with limited laboratory facilities. EIA may not differentiate between HSV types.
- Cytological examination (Tzanck and Papanicolaou smears) has modest specificity and sensitivity and is not recommended for diagnosis (Ib, A).

HSV type-specific serology

- Serological testing is not routinely recommended in asymptomatic patients (IV, C), but is indicated in the following groups:^{1,12,13,14,15,16,17}
 - History of recurrent or atypical genital disease when direct virus detection methods have been negative (III, B). HSV-2 antibodies are supportive of a diagnosis of genital herpes; HSV-1 antibodies do not differentiate between genital and oro-pharyngeal 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.
 - 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).
- Testing of asymptomatic pregnant women is not routinely recommended, but is indicated when there is a history of genital herpes in the partner (IIb, B).^{18,19,20} HSV-1 and/or HSV-2 seronegative women should be counselled about strategies to prevent a new infection with either virus type during pregnancy.
- HSV-2 carriers who engage in high-risk sexual behaviour should be counselled about the increased risk for HIV acquisition (Ia, A).²¹
- Testing of HIV-infected patients is not routinely recommended (IV, C). Although HSV-2 seropositivity increases the risk of HIV transmission and frequent HSV recurrences augment HIV replication, there is limited evidence to inform the management of HSV-2 co-infection in HIV-infected patients without symptoms of genital herpes.^{19,22,23}
- Limited data suggests an increased risk of perinatal HIV transmission among HSV-2 seropositive HIV-infected women.^{24,25} As evidence is not consistent, testing of HIV-positive pregnant women is not routinely recommended (IV, C).²⁶
- HSV serological assays should be used that detect antibodies against the antigenically unique glycoproteins gG1 and gG2.^{11,27} Non type-specific HSV antibody assays are of no value in the management of genital herpes.

- Western blot (WB) is the diagnostic gold-standard. It is >97% sensitive and >98% specific, but is labour-intensive and not commercially available.^{28,29}
- Several commercial (e.g. Focus HerpeSelect ELISA and Immunoblot; Kalon HSV-2 assay) and in-house assays are available, with reported sensitivities >95% and generally high specificities. Specificity, however, can vary significantly in different populations (ranging from as low as 40% to >96%).^{30,31,32,33,34,35,36,37,38,39} False negative results are more likely to occur in early infection and can be resolved by repeat testing. False positive results have been observed in populations with low prevalence and in some African cohorts.⁴⁰ Rapid point of care tests are available (e.g., Biokit HSV-2 assay, previously POCKit™ HSV-2, with sensitivity and specificity >92%) and new assays are being developed.⁴¹
- HSV seroprevalence rates, presence of risk factors for genital herpes, and clinical history influence the positive predictive value (PPV) of HSV type-specific serology and should guide testing and result interpretation (III, B).^{13,25-34} Various ELISA interpretation algorithms are being evaluated. Currently, when using the Focus HSV-2 ELISA in a low risk or heterogeneous setting, the index value for interpreting positivity should be raised from >1.1 to ≥3.5 (IIa, B), taking into account that this reduces sensitivity for both early and established infection.^{29,30,33} Samples with values between 1.1 and 3.5 should undergo confirmation by an alternative method (e.g., Biokit HSV-2 or Kalon ELISA) (IIa, B). The specificity of the Kalon assay improves by raising the cut off to 1.5 (IIa, B). The assay has performed comparatively or better than the Focus ELISA in comparative studies.^{32,34} Concordance between the Focus ELISA and the Kalon assay is 99% using a Focus assay cut off of 3.5.³³
- Type-specific HSV IgG becomes detectable 2 weeks to 3 months after the onset of symptoms and is commonly negative in early presentations.²⁵ Where clinically indicated, follow-up samples should be taken to demonstrate seroconversion (IIa, B). HSV IgM testing substantially increased the ability to detect early infection in patients who lack detectable IgG (IIb, B).⁴² HSV IgM testing however has limited availability in routine diagnostic settings.

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 5 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 episode (Ib, A).^{43,44} No therapy alters the natural course of genital herpes infection.

Topical agents are less effective than oral agents and cannot be recommended (IV, C).

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 five days – are:

- Aciclovir 200 mg five times a day, or
- Aciclovir 400 mg three 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. Patients with sustained systemic symptoms, new lesion development, and complicated disease, should continue therapy beyond five days.

Supportive measures

Saline bathing and the use of appropriate analgesia are recommended. Although the potential for sensitisation exists in the use of topical anaesthetic agents, lignocaine is a rare sensitiser and can be used safely in genital herpes in the form of gel or ointment.⁴⁵ Benzocaine, however, is a potent sensitiser and should not be used. (IV, C)

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).^{46,47,48} 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 typically occurs during the second week. This is characterised by the recrudescence of local symptoms. Candida is most often implicated and is easily diagnosed and treated.

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 10-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 possible source of infection
- 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, in pregnancy, to the foetus. The patient should be counselled to inform the obstetrician or midwife.
- The possibility of partner notification

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 co-existent.

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. 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).^{49,50,51} Head-to-head studies of their effects show no advantage of one therapy over another, or the advantage of extended 5-day treatment over ultra-short therapy. Prodrugs offer simplified twice-a-day dosing. It is likely that patient-initiated treatment started within 24 hours is most likely to be effective. Aborted lesions have been documented in up to one third of patients with early treatment.⁵² To ensure prompt treatment, patients should be advised to carry a small quantity of drugs at all times.

The recommended regimens – all for five days – are:

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

Short course therapies are:

- Aciclovir 800 mg three times daily for 2 days, or⁵³
- Famciclovir 1 gram twice daily for one day, or⁵⁴
- Valaciclovir 500 mg twice daily for 3 days (Ib, A).^{55,56,57,58,59}

Suppressive therapy

The majority of trials of suppressive therapy have been done in patients with a recurrence rate equivalent to ≥ 6 recurrences/annum. However, it is likely that patients with a lower rate of recurrence will also 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 and the impact of disease on the individual 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).⁶⁰ Safety and resistance data on patients on long-term therapy now extends to over 18 years of continuous surveillance. 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 4 times a day was marginally superior to 400 mg twice daily ($p < 0.02$) (IIb, B).⁶¹ However, ability to comply with a 4 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 per annum, 250 mg b.d. or 1 g once a day is required.⁶²

No major clinically significant differences between suppressive therapy with valaciclovir (500 mg daily) and famciclovir (250 mg twice daily) have been documented (IV, C).⁶³ 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 may occur with valaciclovir.

Therapy should be discontinued after a maximum of a year of continuous antiviral therapy to reassess recurrence frequency, providing the patient is willing to accept this course of action. 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.

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 10 or fewer recurrent episodes per year) significantly reduced transmission in serodiscordant couples (Ib, A).⁶⁴ Hence, suppressive valaciclovir therapy may be considered in addition to the use of condoms and selective sexual abstinence.

SPECIAL SITUATIONS

Management of HSV in the immunocompromised and HIV positive patient

Management of initial episode HSV

There is 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 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 counts.

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. In addition, if fulminant disease ensues that intravenous aciclovir be substituted. Recommended initial doses:

- Aciclovir 200-400mg five times daily, 400mg-800mg tds (IV,C)
- Valaciclovir 500-1g bd (IV,C)
- Famciclovir 250-500mg tid (IV,C)

Treatment should be given for 5-10 days or at least until all lesions have re-epithelialized – this will often exceed the usual 10 day duration of treatment that is given to HIV negative patients.

Management of recurrent disease

A number of trials of antiviral therapy in the immunocompromised have been reported.

Duration of therapy

It is likely that 5 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.⁶⁵ Shorter courses of therapy may be adequate in those with good CD4 counts (>500) although only one trial with famciclovir has reported this effect (1b,B).⁵⁴

Dosage of antivirals

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 5 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 is effective and well tolerated. All three agents have been trialled. Standard suppressive doses of aciclovir are effective. Valaciclovir is more effective when given twice daily (500mg bid) compared to once daily dosing (1000mg).⁶⁶ The valaciclovir 500mg once daily dose has not been evaluated in the HIV positive patient. Trial data for the efficacy of high dose famciclovir is only available over much shorter durations.⁶⁷ 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 (400mg qid) and more recently at standard dose regimens.^{66,68,69} For valaciclovir a number of studies looked at the value of valaciclovir for the suppression of recurrent genital herpes.⁶⁶ High dose valaciclovir (2g qid) has been studied and reported in HIV positives, 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 reported. These trials indicate that use of oral aciclovir at standard dose and valaciclovir at 1g od and 500mg bd is associated with little or no adverse effect or toxicity as compared to the non HIV positive. High dose valaciclovir (8g daily) has been associated with Microangiopathic Haemolytic Uraemic syndrome.⁷⁰

Dosage

The best evidence to achieve suppression exists for valaciclovir 500mg bd, aciclovir 400mg bd (1b, A) and that if these agents are not successful at controlling disease that famciclovir 500mg bd could be tried (IIa,B).

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 immune reconstitution inflammatory syndrome (IRIS) following combination antiretroviral therapy. Algorithms for treatment in such situations are shown in Figure 1.

HSV suppression to limit HIV progression

Suppressive antiviral therapy has been shown to decrease the levels of HIV viraemia in those patients with detectable HIV viral loads.⁷¹ 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 counts above 350) has shown that standard doses of suppressive antiviral therapy (aciclovir 400mg bd) will sustain CD4 counts above accepted treatment levels and this effect reduced the need for HAART at 2 years by 16% in the treatment group.⁷²

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 patients:

- Asymptomatic shedding plays a major role in the transmission of HSV infection.
- Partner notification is an effective way of detecting uninfected or asymptomatic individuals 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. It may be possible to reduce the risks of transmission by educating patients to recognise symptomatic recurrences.

- Virus transmission can be reduced either with suppressive antiviral treatment or by using condoms.

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 400mg t.i.d. from 36 weeks gestation may prevent HSV lesions at term and hence the need for delivery by Caesarean section (Ib, B).^{73,74,75,76,77,78}

Third trimester acquisition (IV, C)

- Caesarean section should be considered for all women, particularly those developing symptoms within 6 weeks of delivery, as the risk of viral shedding in labour is very high (Ib, B).
- Daily suppressive aciclovir 400mg t.i.d. from 36 weeks gestation may prevent HSV lesions at term.
- 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.⁷⁹

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.

- 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 400mg tid from 36 weeks gestation may prevent HSV lesions at term and hence the need for delivery by Caesarean section (Ia, A).⁸⁰
- 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.⁸¹
- The utility of taking cultures or PCR at delivery, in order to identify women who are asymptotically shedding HSV, is unproven.

Management of recurrent HSV in early pregnancy

Although the safety of aciclovir in early 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.^{82,83}

- Women who are HIV antibody positive and have a history of genital herpes should be offered daily suppressive aciclovir 400mg t.i.d. 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.⁸⁴

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 an anogenital lesion, has not been associated with a rise in numbers of neonatal HSV cases (III, B).⁸⁵ 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 fetal/neonatal adverse effects, other than transient neutropenia in data from the aciclovir pregnancy.⁸⁶ 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.⁸⁷ 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 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 conscientious use of condoms during pregnancy especially in the last trimester of pregnancy, abstaining from sex at the time of lesional recurrences and in the last six weeks of pregnancy.
- 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.
- 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

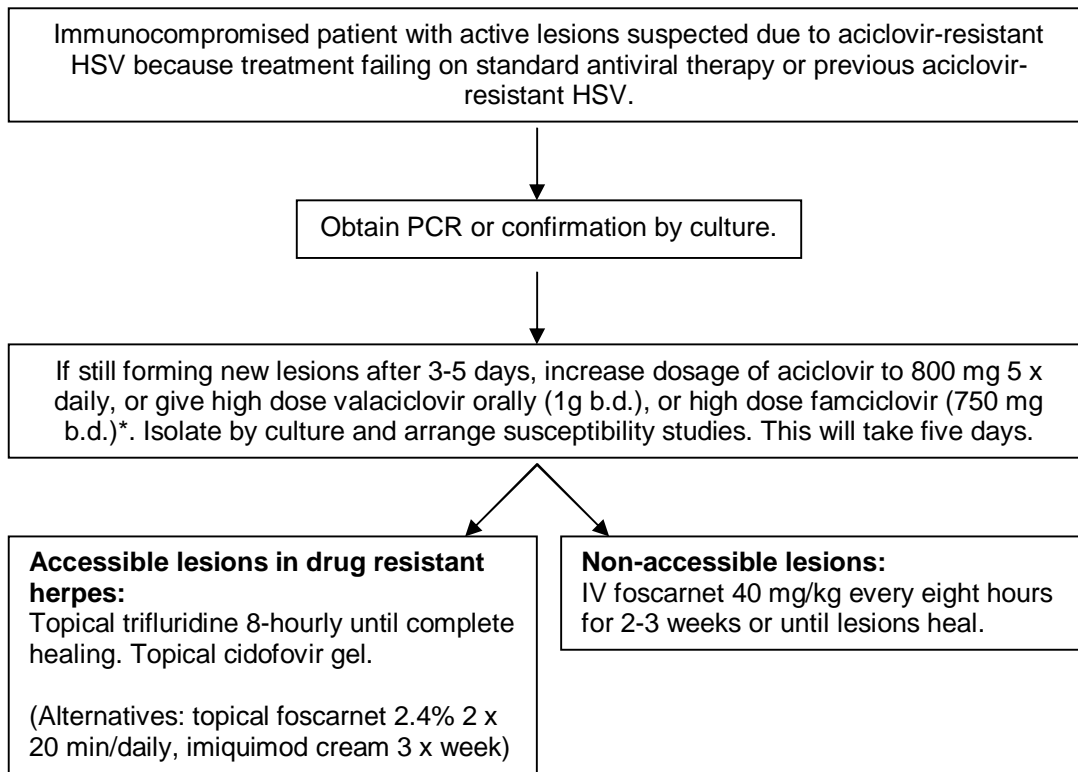
- The paediatrician should be informed.
- HSV culture of urine and stool, from the oropharynx, eyes and surface sites, should be taken to allow early identification of infected babies
- The potential benefits and risks of starting intravenous aciclovir without waiting for the results of these cultures 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 culture collected 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.

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



*All HSV strains resistant to aciclovir are also resistant to valaciclovir

Appendix I: Levels of evidence and grading of recommendations

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

References

- ¹ Casper C, Wald A. Condom use and the prevention of genital herpes acquisition. *Herpes*. 2002 Apr; 9(1):10-4
- ² Wald A, Langenberg AGM, Krantz E, Douglas JM, Handsfield HH, DiCarlo RP, Adimora AA, Izu AE, Morrow RA, Corey L. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med*. 2005 Nov 15;143(10):707-13
- ³ Gupta R, Warren T, Wald A. Genital herpes. *Lancet*. 2007;370:2127-37.
- ⁴ Koutsky LA, Stevens CE, Holmes KK, Ashley RL, Kiviat NB, Critchlow CW, Corey L. Underdiagnosis of genital herpes by current clinical and viral-isolation procedures. *N Engl J Med* 1992;326:1533-9.
- ⁵ Wald A, Huang ML, Carrell D, Selke S, Corey L. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. *J Infect Dis* 2003;188:1345-51.
- ⁶ Ramaswamy M, McDonald C, Smith M, Thomas D, Maxwell S, Tenant-Flowers M, Geretti AM. Diagnosis of genital herpes by real-time PCR in routine clinical practice. *Sex Transm Infect* 2004;80:406-10.
- ⁷ Van Doornum GJ, Guldemeester J, Osterhaus AD, Niesters HG. Diagnosing herpesvirus infections by real-time amplification and rapid culture. *J Clin Microbiol* 2003;41:576-80.
- ⁸ Geretti AM. Genital herpes. *Sex Transm Infect* 2006;82 Suppl 4:iv31-4.
- ⁹ Verano L, Michalski FJ. Herpes simplex virus antigen direct detection in standard virus transport medium by Du Pont HerpChek enzyme-linked immunosorbent assay. *J Clin Microbiol*. 1990;28:2555-8.
- ¹⁰ Slomka MJ, Emery L, Munday PE, Moulds M, Brown DW. A comparison of PCR with virus isolation and direct antigen detection for diagnosis and typing of genital herpes. *J Med Virol* 1998;55:177-83.
- ¹¹ Cone RW, Swenson PD, Hobson AC, Remington M, Corey L. Herpes simplex virus detection from genital lesions: a comparative study using antigen detection (HerpChek) and culture. *J Clin Microbiol* 1993;31:1774-6.
- ¹² Munday PE, Vuddamalay J, Slomka MJ, et al. Role of type specific herpes simplex virus serology in the diagnosis and management of genital herpes. *Sex Transm Infect* 1998; 74:175-8.
- ¹³ Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. *Clin Microbiol Rev* 1999;12:1-8.
- ¹⁴ Malkin JE. Herpes simplex virus. Who should be tested. *Herpes* 2002;9:31.
- ¹⁵ Copas AJ, Cowan FM, Cunningham AL, Mindel A. An evidence based approach to testing for antibody to herpes simplex virus type 2. *Sex Transm Infect* 2002;78:430-4.
- ¹⁶ Corey L, Wald A, Patel R, et al. Once daily valaciclovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. 2004;350:11-20.
- ¹⁷ Ramaswamy M, McDonald C, Sabin C, Tenant-Flowers M, Smith M, Geretti AM. The epidemiology of genital infection with herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in genitourinary medicine attendees in inner London. *Sex Transm Infect* 2005;81:306-8.
- ¹⁸ Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997;337:509-515.
- ¹⁹ Rouse DJ, Stringer JSA. An appraisal of screening for maternal type-specific herpes simplex antibodies to prevent neonatal herpes. *Am J Obstet Gynecol* 2000;183:400-6.
- ²⁰ Tita AT, Grobman WA, Rouse DJ. Antenatal herpes serologic screening: an appraisal of the evidence. *Obstet Gynecol*. 2006;108:1247-53.
- ²¹ Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* 2002;185:45-52.
- ²² Strick LB, Wald A, Celum C. Management of herpes simplex virus type 2 infection in HIV type 1-infected persons. *Clin Infect Dis*. 2006;43:347-56.
- ²³ Ramaswamy M, Geretti AM. Interactions and management issues in HSV and HIV coinfection. *Expert Rev Infect Ther* 2007;5:231-43.
- ²⁴ Drake AL, John-Stewart GC, Wald A, et al. Herpes simplex virus type 2 and risk of intrapartum human immunodeficiency virus transmission. *Obstet Gynecol*. 2007;109:403-9.
- ²⁵ Bollen LJ, Whitehead SJ, Mock PA, et al. Maternal herpes simplex virus type 2 coinfection increases the risk of perinatal HIV transmission: possibility to further decrease transmission? *AIDS*. 2008;22:1169-76.

-
- ²⁶ Chen KT, Tuomala RE, Chu C, et al. No association between antepartum serologic and genital tract evidence of herpes simplex virus-2 coinfection and perinatal HIV-1 transmission. *Am J Obstet Gynecol.* 2008;198:399. e1-5.
- ²⁷ Ashley RL. Performance and use of HSV type-specific serology test kits. *Herpes* 2002;9:38-45.
- ²⁸ Ashley RL, Benedetti J, Corey L. Humoral immune response to HSV-1 and HSV-2 viral proteins in patients with primary genital herpes. *J Med Virol* 1985;17:153–166
- ²⁹ Ashley RL. Type-specific antibodies to HSV-1 and 2: review of methodology. *Herpes* 1998;5:33–38.
- ³⁰ Smith JS, Bailey RC, Westreich DJ, et al. Herpes simplex virus type 2 antibody detection performance in Kisumu, Kenya, using the Herpesselect ELISA, Kalon ELISA, Western blot and inhibition testing. *Sex Transm Infect.* 2009;85:92-6.
- ³¹ Gopal R, Gibbs T, Slomka MJ, et al. A monoclonal blocking EIA for herpes simplex virus type 2 antibody: validation for seroepidemiological studies in Africa. *J Virol Methods* 2000; 87:71-80.
- ³² Morrow RA, Friedrich D, Krantz E. Performance of the Focus and Kalon enzyme-linked immunosorbent assays for antibodies to herpes simplex virus type 2 glycoprotein G in culture-documented cases of genital herpes. *J Clin Microbiol* 2003; 41:5212-4.
- ³³ Van Dyck E, Buve A, Weiss HA, et al. Performance of commercially available enzyme immunoassays for detection of antibodies against herpes simplex virus type 2 in African populations. *J Clin Microbiol* 2004;42:2961-5.
- ³⁴ Golden MR, Ashley-Morrow R, Swenson P, Hogrefe WR, Handsfield HH, Wald A. Herpes simplex virus type 2 (HSV-2) Western blot confirmatory testing among men testing positive for HSV-2 using the focus enzyme-linked immunosorbent assay in a sexually transmitted disease clinic. *Sex Transm Dis.* 2005;32:771-7.
- ³⁵ Morrow RA, Friedrich D, Meier A, Corey L. Use of "biokit HSV-2 Rapid Assay" to improve the positive predictive value of Focus HerpeSelect HSV-2 ELISA. *BMC Infect Dis.* 2005;5:84. doi:10.1186/1471-2334-5-84.
- ³⁶ Ashley Morrow R, Krantz E, Friedrich D, Wald A. Clinical correlates of index values in the focus HerpeSelect ELISA for antibodies to herpes simplex virus type 2 (HSV-2). *J Clin Virol.* 2006;36:141-5.
- ³⁷ Nascimento MC, Ferreira S, Sabino E, et al. Performance of the HerpeSelect (Focus) and Kalon enzyme-linked immunosorbent assays for detection of antibodies against herpes simplex virus type 2 by use of monoclonal antibody-blocking enzyme immunoassay and clinicovirological reference standards in Brazil. *J Clin Microbiol.* 2007;45:2309-11.
- ³⁸ LeGoff J, Mayaud P, Gresenguet G, et al. Performance of HerpeSelect and Kalon assays in detection of antibodies to herpes simplex virus type 2. *J Clin Microbiol.* 2008;46:1914-8.
- ³⁹ Gamiel JL, Tobian AA, Laeyendecker OB, et al. Improved performance of enzyme-linked immunosorbent assays and the effect of human immunodeficiency virus coinfection on the serologic detection of herpes simplex virus type 2 in Rakai, Uganda. *Clin Vaccine Immunol.* 2008;15:888-90.
- ⁴⁰ Smith JS, Bailey RC, Westreich DJ, et al. Herpes simplex virus type 2 antibody detection performance in Kisumu, Kenya, using the Herpesselect ELISA, Kalon ELISA, Western blot and inhibition testing. *Sex Transm Infect.* 2009;85:92-6.
- ⁴¹ Laderman EI, Whitworth E, Dumaul E, et al. Rapid, sensitive, and specific lateral-flow immunochromatographic point-of-care device for detection of herpes simplex virus type 2-specific immunoglobulin G antibodies in serum and whole blood. *Clin Vaccine Immunol.* 2008;15:159-63.
- ⁴² Morrow R, Friedrich D. Performance of a novel test for IgM and IgG antibodies in subjects with culture-documented genital herpes simplex virus-1 or -2 infection. *Clin Microbiol Infect* 2006;12:463-9
- ⁴³ Corey L, Benedetti J, Critchlow C, et al. Treatment of primary first-episode genital herpes simplex virus infections with aciclovir: results of topical, intravenous and oral therapy. *J Antimicrob Chemother* 1983;12(suppl B):79-88.
- ⁴⁴ Fife KH, Barbarash RA, Rudolph T, DeGregorio B, Roth R. Valaciclovir versus aciclovir in the treatment of first-episode genital herpes infection. Results of an international multicenter, double-blind, randomized clinical trial. The Valaciclovir International Herpes Simplex Virus Study Group. *Sex Transm Dis* 1997;24:481-6.

-
- ⁴⁵ Weightman, W.; Turner, T.; Allergic contact dermatitis from lignocaine: report of 29 cases and review of the literature; *Contact Dermatitis* 1998;39:265
- ⁴⁶ Carney, O Ross, E Bunker, C, Ikkos, G and Mindel, A. *A prospective study of the psychological impact on patients with a first episode of genital herpes*. *Genitourinary Medicine*, 1994, 70, 40-45
- ⁴⁷ Patel R, Tyring S, Price MJ, et al. Impact of suppressive antiviral therapy on the health related quality of life of patients with recurrent genital herpes infection. *Sex Transm Infect* 1999; **75**: 398-402
- ⁴⁸ Green J, Kocsis A. *Psychological factors in recurrent genital herpes*. *Genitourinary Medicine*, 1997; **73**: 253-259
- ⁴⁹ Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral aciclovir in the treatment of initial and recurrent genital herpes. *Lancet* 1982;ii:571-3
- ⁵⁰ Spruance SL, Tyring TK, DeGregorio B, Miller C, Beutner K and the Valaciclovir study group. A large-scale, placebo controlled, dose ranging trial of peroral valaciclovir for episodic treatment of recurrent herpes genitalis. *Arch Intern Med* 1996;**156**:1729-35.
- ⁵¹ Sacks SL, Aoki FY, Diaz-Mitoma F, Sellors J, Shafran SD, for the Canadian Famciclovir Study. Patient-initiated, twice daily, oral famciclovir for early recurrent genital herpes: a randomized, double-blind multicenter trial. *JAMA* 1996;**276**:44-9
- ⁵² Spruance SL, Overall JC, Kern ER, et al. The natural history of recurrent herpes simplex labialis: implications for antiviral therapy. *N Engl J Med* 1977(297):69-75
- ⁵³ Wald A, Carrell D, Remington M, et al. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis* 2002 34(7):944-8
- ⁵⁴ Bodsworth N, Bloch M, McNulty A, 2-day versus 5-day famciclovir as treatment of recurrences of genital herpes: results of the FaST study, *Sexual Health* 2008 5(3)219-225
- ⁵⁵ Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of aciclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis* 2002;**34**:944-8.
- ⁵⁶ Aoki FY, Tyring S, Diaz-Mitoma F, Gross G, Gao J, Hamed K. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2006;**42**:8-13
- ⁵⁷ Abudalu M, Tyring S, Koltun W, Bodsworth N, Hamed K. Single-day, patient-initiated famciclovir therapy versus 3-day valaciclovir regimen for recurrent genital herpes: a randomized, double-blind, comparative trial. *Clin Infect Dis* 2008;**47**:651-8
- ⁵⁸ Leone PA, Trottier S, Miller JM. Valaciclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. *Clin Infect Dis* 2002;**34**:958-62.
- ⁵⁹ Strand A, Patel R, Wulf HC, Coates KM and The International Valaciclovir Study Group. Aborted genital herpes simplex virus lesions: findings from a randomised controlled trial with valaciclovir. *Sex Transm Infect* 2002;**78**:435-9
- ⁶⁰ Mertz GJ, Jones CC, Mills J et al. Long-term aciclovir suppression of frequently recurring genital herpes simplex virus infection. A multicenter double-blind trial. *JAMA* 1988;**260**:201-6
- ⁶¹ Mindel A, Faherty A, Carney O, Patou G, Freris M, Williams P. Dosage and safety of long-term suppressive aciclovir therapy for recurrent genital herpes. *Lancet* 1988;**331**:926-8
- ⁶² Lebrun-Vignes B et al. A meta-analysis to assess the efficacy of oral antiviral treatment to prevent genital herpes outbreaks. *J Am Acad Dermatol* 2007;**57**:238-46
- ⁶³ Geretti AM. Genital herpes. *Sex Transm Infect* 2006;**82** Suppl 4:iv31-4.
- ⁶⁴ Corey L, Wald A, Patel R et al. Once-daily valaciclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004;**350**:11-20
- ⁶⁵ Romanowski B, Aoki FY, Martel AY, Lavender EA, Parsons JE, Saltzman RL. Efficacy and safety of famciclovir for treating mucocutaneous herpes simplex infection in HIV infected individuals. *AIDS* 2000;**14**:1211-1217
- ⁶⁶ Conant MA, Schacker TW, Murphy RL, Gold J, Crutchfield LT, Crooks RJ; International Valaciclovir HSV Study Group. *Int J STD AIDS*. 2002 Jan;**13**(1):12-21.
- ⁶⁷ Schacker T, Hu HL, Koelle DM, Zeh J, Saltzman R, Boon R, Shaughnessy M, Barnum G, Corey L. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. *Ann Intern Med*. 1998 Jan 1;**128**(1):21-8
- ⁶⁸ Youle MS, Gazzard BG, Johnson MA, Cooper DA, Hoy JF, Busch H et al. Effects of high-dose oral acyclovir on herpesvirus disease and

survival in patients with advanced HIV disease: a double-blind, placebocontrolled study. *AIDS* 1994;8:641–649

⁶⁹ Cooper DA, Pehrson PO, Pedersen C, Moroni M,

Oksenhendler E, Rozenbaum W et al The efficacy and safety of zidovudine alone or as cotherapy with aciclovir for the treatment of patients with AIDS and AIDS-related complex: a double-blind, randomized trial. *AIDS* 1993;7:197–207

⁷⁰ Bell WB, Chulay JD, Feinberg JE. Manifestations resembling thrombomicroangiopathy in patients with advanced human immunodeficiency virus (HIV) disease in a cytomegalovirus prophylaxis trial (ACTG 204). *Medicine (Baltimore)* 1997;76:369–380.

⁷¹ Delany S, N Mlaba N, Clayton T, et al. Impact of aciclovir on genital and plasma HIV-1 RNA in HSV-2/HIV-1 co-infected women: a randomized placebo-controlled trial in South Africa. *AIDS* 2009; 23: 461-469

⁷² Lingappa, JR; Baeten, JM; Wald, A; Daily aciclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. *Lancet*. 2010; 375:9717:824-833

⁷³ Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. *Obstet Gynecol*. 2003;102(6):1396–1403.

⁷⁴ Watts DH, Brown ZA, Money D, et al. A doubleblind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of Herpes simplex virus shedding and cesarean delivery. *Am J Obstet Gynecol*. 2003;188(3):836–843

⁷⁵ Scott LL, Hollier LM, McIntire D, Sanchez PJ, Jackson GL, Wendel GD Jr. Acyclovir suppression to prevent recurrent genital herpes at delivery. *Infect Dis Obstet Gynecol*. 2002;10(2):71–77

⁷⁶ Brocklehurst P, Kinghorn G, Carney O, et al. A randomised placebo-controlled trial of suppressive acyclovir in late pregnancy in women with recurrent genital herpes infection. *Br J Obstet Gynaecol*. 1998; 105(3):275–280

⁷⁷ Scott LL, Sanchez PJ, Jackson GL, Zeray F, Wendel GD Jr. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. *Obstet Gynecol*. 1996;87(1):69–73

⁷⁸ Braig S, Luton D, Sibony O, et al. Acyclovir prophylaxis in late pregnancy prevents recurrent genital herpes and viral shedding. *Eur J Obstet Gynecol Reprod Biol*. 2001;96(1):55–58

⁷⁹ Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. *Cochrane Database of Systematic Reviews* 2008, Issue 1

⁸⁰ Gardella C, Brown ZA, Wald A et al. Poor correlation between genital lesions and detection of herpes simplex virus in women in labor. *Obstet. Gynecol*. 2005;106: 268-274

⁸¹ Chen KT, Segu M, Lumey LH et al. Genital herpes simplex virus infection and perinatal transmission of human immunodeficiency virus. *Obstet Gynecol* 2005;106:1341-8

⁸² Drake AL, John-Stewart GC, Wald A et al. Herpes simplex virus type 2 and the risk of intrapartum human immunodeficiency virus transmission. *Obstet Gynecol* 2007; 10;403-9

⁸³ Chen KT, Tuomala RE, Chu C et al. No association between antepartum serologic and genital tract evidence of herpes simplex virus-2 coinfection and perinatal HIV-1 transmission. *Am J Obstet Gynecol* 2008 Apr;198(4)

⁸⁴ Poeran J, Wildschut H, Gaytant M, Galama J, Steegers E, van der Meijden W. The incidence of neonatal herpes in The Netherlands; *J Clin Virol*. 2008 Aug;42(4):321-5

⁸⁵ Acyclovir and Valacyclovir in Pregnancy Registry final report. April 1999. Available at: <http://pregnancyregistry.gsk.com/acyclovir.html>

⁸⁶ Andrews WW, Kimberlin DF, Whitley R, Cliver S, Ramsay PS, Deeter R. Valacyclovir therapy to reduce recurrent genital herpes in pregnant women *Am J Obstet Gynecol* 2006; 194:774-8

⁸⁷ Sheffield JS, Hill JB, Hollier LM, Laibl VR, Roberts SW, Sanchez PJ, Wendel GD Jr Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomised clinical trial. *Obstet Gynecol* 2006; 108: 141 –147