

## **2007 National Guideline for the Management of Genital Herpes**

### **Clinical Effectiveness Group (British Association for Sexual Health and HIV)**

#### **Objective**

The overall aim of the guideline is to prevent morbidity (physical and psychological) associated with genital herpes and ultimately to reduce transmission and prevalence particularly as genital herpes is associated with enhanced transmission of HIV.

The guideline provides recommendations on the management of adults with genital herpes in the UK, including pregnant women and individuals co-infected with HIV.

Recommendations include diagnostic tests, management of the primary or first episode of genital herpes and recurrences, effectiveness of therapy, prophylaxis, prevention of mother to child transmission and transmission between partners as well as patient centered counselling.

#### **Stakeholder development**

The current guideline has been developed by the Herpes Simplex Advisory Panel which is a special interest group of BASHH. The Panel incorporates specialist clinicians, virologists, health advisers, nurses, clinical psychologist and a representative from the Herpes Viruses Association (a self help organisation). The draft guideline was placed on the BASHH website for a 3 month consultation period.

The Process was overseen by the Clinical Effectiveness Group of BASHH. This is the second revision of the guideline first written in 1999.

#### **Rigour of development**

##### **Search Strategy**

This review was updated by searching PubMed from 1999-2007 for publications in English using the search terms/Mesh headings:

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

Neonatal herpes: "Neonatal herpes", "pregnancy complications – infectious", "herpes near pregnancy" free text.

A search of the Cochrane Library was also searched using the MeSH terms: "randomized controlled trials", "Genital Herpes", "herpes genitalis".

##### **Definitions**

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

**Primary infection:** first infection with either HSV-1 or HSV-2 in an individual with no pre-existing antibodies to either type.

**Non-primary infection:** first infection with either HSV-1 or HSV-2 in an individual with pre- existing antibodies to the other type.

**Recurrent episode:** recurrence of clinical symptoms due to reactivation of pre-existent HSV-1 or HSV-2 infection after a period of latency.

## GENITAL HERPES

### Aetiology

- Herpes simplex virus type 1 (HSV-1, the usual cause of oro-labial herpes) or
- Herpes simplex virus type 2 (HSV-2, historically associated with sexual transmission)

### Natural History

- Infection may be primary or non-primary. Disease episodes may be initial or recurrent (figure 1) and symptomatic or asymptomatic. It is likely that the majority of infections are acquired subclinically as at least 80% of persons seropositive for HSV type-specific antibodies are unaware of that they have been infected.
- Prior infection with HSV-1 modifies the clinical manifestations of first infection by HSV-2<sup>1</sup>.
- After childhood, symptomatic primary infection with HSV-1 is equally likely to be acquired in the genital area or oral areas<sup>2,2A</sup>.
- Primary genital herpes in the UK is equally likely to be caused by HSV-1 as by HSV-2.
- Following primary infection, the virus becomes latent in local sensory ganglia, periodically reactivating to cause symptomatic lesions or asymptomatic, but infectious, viral shedding.
- The median recurrence rate after a symptomatic first episode is 0.34 recurrences/ month for HSV-2 and is four times more frequent than the recurrence rate for HSV-1<sup>3</sup>. Recurrence rates decline over time in most individuals, although this pattern is variable<sup>4</sup>.
- The majority of individuals found to be seropositive for HSV-2 type-specific antibodies subsequently develop symptomatic lesions<sup>5</sup>. In some of these individuals, the number of days when virus is shed asymptotically exceeds the number of days of symptomatic shedding associated with lesions. Virus can be shed asymptotically from the external genitalia, the anorectum, the cervix, and urethra.
- In HIV positive HSV-2 seropositive individuals, both symptomatic and asymptomatic shedding are increased, especially in those with low CD4 counts and those who are also seropositive for HSV-1<sup>6,7</sup>.

## Clinical Features

### Symptoms

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

### Signs

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

### Complications

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

### Atypical GH

- The lesions of recurrent episodes may be small, and may resemble non-specific erythema, erosions or fissures.
- In the United States, only about 20% of those patients who present to physicians with genital symptoms receive a correct diagnosis of GH <sup>4</sup>.

## Diagnosis

For a detailed discussion of diagnostic methods for genital herpes please refer to the "Sexually Transmitted Infection Screening and Testing Guidelines" (2006 edition) produced by the Screening Guidelines Steering Committee of the BASHH Clinical Effectiveness Group.

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

### Virus detection and characterization

- The confirmation and characterisation of the infection and its type, by direct detection of HSV in genital lesions, are essential for diagnosis, prognosis, counselling, and management (IV, C).

- Methods should be used that directly demonstrate HSV in swabs taken from the base of the genital lesion. (1b, A).
- Virus typing to differentiate between HSV-1 and HSV-2 should be obtained in all patients with newly diagnosed genital herpes (III, B).
- HSV isolation in cell culture is the current routine diagnostic method in the UK<sup>7A</sup>. Virus culture is slow, labour-intensive and expensive. Specificity is virtually 100%, but levels of virus shedding, quality of specimens, and sample storage and transport conditions influence sensitivity<sup>8-10</sup>. Delayed sample processing and lack of specimen refrigeration after collection and during transport significantly reduce the yield of virus culture at all stages of the infection<sup>9,10</sup>.
- HSV DNA detection by polymerase chain reaction (PCR) increases HSV detection rates by 11-71% compared with virus culture.<sup>8-10</sup> PCR-based methods allow less stringent conditions for sample storage and transport than virus culture and new real-time PCR assays are rapid and highly specific. Real-time PCR is recommended as the preferred diagnostic method for genital herpes (1b, A). PCR assays must be appropriately validated before clinical use and their availability should be discussed with service providers.

## Serology

- Testing for HSV type-specific antibodies can be used to diagnose HSV infection<sup>7A</sup>. The detection of HSV-1 IgG or HSV-2 IgG or both, in a single serum sample represents HSV infection with HSV at some time. It is difficult to say whether the infection is recent as IgM detection is unreliable and avidity studies are not commonly available. Collection of serum samples a few weeks apart can be used to show seroconversion and, hence, recent primary infection. HSV-2 antibodies are indicative of genital herpes. HSV-1 antibodies do not differentiate between genital and oropharyngeal infection.
- Many commercial tests for HSV antibodies are not type-specific and are of no value in the management of genital herpes<sup>11</sup>. Assays should be used that detect antibodies against the antigenically unique glycoproteins gG1 and gG2 (III, B)<sup>11,12</sup>.
- Western blot is the diagnostic gold-standard, but it is not commercially available. Several commercial assays, as well as validated in-house methods, are available which show 91-99% sensitivity and 92-98% specificity relative to Western blot in sexually active adults<sup>12,13</sup>.
- Caution is needed in interpreting serology results because even highly sensitive and specific assays have poor predictive values in low prevalence populations (Table 1). Local epidemiological data and patient demographic characteristics should guide testing and result interpretation (III, B)<sup>14</sup>.
- In patients with a low likelihood of genital herpes, a positive HSV-2 antibody result should be confirmed in a repeat sample or by a different assay (III, B).
- Type-specific immune responses usually take several weeks to develop<sup>12</sup>. The median time to antibody detection may vary between different assays. False negative results may be obtained early after infection, requiring follow-up samples to demonstrate seroconversion.

- The value of routine screening of all genitourinary medicine clinic attendees or antenatal patients and their partners for HSV antibodies remains to be established. Serology may be helpful in the following situations (III, B):
  - recurrent genital disease of unknown cause
  - counselling patients with initial episodes of disease, including pregnant women
  - investigating asymptomatic partners of patients with genital herpes, including pregnant women

## Management

### First Episode Genital Herpes

#### General advice

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

#### Antiviral drugs

- Oral antiviral drugs are indicated within 5 days of the start of the episode and while new lesions are still forming.
- Aciclovir, valaciclovir, and famciclovir all reduce the severity and duration of episodes (Ib, A) <sup>15, 16, 17</sup>.
- Antiviral therapy does not alter the natural history of the disease <sup>18</sup>.
- Topical agents are less effective than oral agents.
- Combined oral and topical treatment is of no benefit.
- Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting.
- There is no evidence for benefit from courses longer than five days. However, it may be prudent to review the patient after 5 days and continue therapy if new lesions are still appearing at this time.

#### Recommended regimens (all for five days):

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

## Management of complications

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

## Recurrent Genital Herpes

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

## Episodic antiviral treatment (Ia, A)

- Oral aciclovir, valaciclovir, and famciclovir reduce the duration (by median of 1-2 days)<sup>19, 20, 21</sup> and severity of recurrent GH.
- Patient initiated treatment started early in an episode is most likely to be effective.
- Recommended regimens (all for five days)
  - Aciclovir 200 mg five times daily
  - Aciclovir 400 mg three times daily for 3-5 days
  - Valaciclovir 500 mg twice daily
  - Famciclovir 125 mg twice daily
- Short course therapies
  - Aciclovir 800mg three times daily for 2days<sup>21a</sup>
  - Famciclovir 1 gram bd for one day<sup>21b</sup>
  - Valaciclovir 500 mg bd for 3 days<sup>21c, 21d</sup>

## Suppressive antiviral therapy

- Patients who have taken part in trials of suppressive therapy have had at least six recurrences per annum. Such patients have fewer or no episodes on suppressive therapy (1b,A). Patients with lower rates of recurrence will probably also have fewer recurrences with treatment<sup>22, 23</sup>.
- Patients should be given full information on the advantages and

disadvantages of suppressive therapy. The decision to start suppressive therapy is a subjective one, balancing the frequency of recurrence with the cost and inconvenience of treatment.

- Patient safety and resistance data for long-term suppressive therapy with aciclovir <sup>24</sup> now extends to over 18 years of continuous surveillance (III, B).
- Recommended regimens (1b, A)
  - Aciclovir 400mg twice daily
  - Aciclovir 200mg four times daily
  - Famciclovir 250mg twice daily<sup>18</sup>
  - Valaciclovir 500mg once daily
- If breakthrough recurrences occur on standard treatment, the daily dosage should be increased eg. Aciclovir 400mg three times daily
- Choice of treatment depends on patient compliance and cost (table 3)
- Suppressive therapy should be discontinued after a maximum of a year to reassess recurrence frequency. The minimum period of assessment should include two recurrences. Patients who continue to have unacceptably high rates of recurrence may restart treatment. (IV, C).
- Short courses of suppressive therapy may be helpful for some patients (IV, C).

### **Asymptomatic Viral Shedding**

- Occurs in individuals with genital HSV-1 and those with genital HSV-2.
- Occurs most commonly in patients with genital HSV-2 infection in the first year after infection
  - in individuals with frequent symptomatic recurrences
  - is an important cause of transmission
  - may be reduced by aciclovir 400 mg twice daily (1b, A) <sup>25</sup>

i

### **Prevention of Transmission**

- Condoms may be partially effective in preventing acquisition of HSV, especially in preventing transmission from infected males to their female sex partners<sup>26</sup>. The efficacy of male condoms in preventing transmission from infected females to uninfected male partners has not been demonstrated, and the efficacy of female condoms to reduce HSV transmission during intercourse has not been assessed.
- Aciclovir, famciclovir, and valaciclovir all suppress symptomatic and asymptomatic viral shedding. These drugs have been shown in clinical trials to reduce asymptomatic HSV shedding by about 80 - 90%. Although the threshold for infection from asymptomatic shedding has not been established, small studies have shown that Valaciclovir appears to suppress asymptomatic shedding better than Famciclovir <sup>26b</sup>. Acyclovir (400 mg twice daily) has been shown to suppress asymptomatic shedding at least as well as Valaciclovir (1000 mg daily) <sup>26c</sup>.

- Suppressive antiviral therapy with valaciclovir 500 mg once daily reduces the rate of acquisition of HSV-2 infection and clinically symptomatic genital herpes in serodiscordant couples. In a randomised trial involving 1484 patients treated for 8 months, 0.5% valaciclovir recipients developed symptomatic infection compared with 2.2% of placebo recipients, and 1.6% compared with 3.2% acquired HSV-2 infection. Although valaciclovir reduced the risk of acquiring symptomatic infection by 75%, approximately 60 people needed to be treated to prevent one transmission.<sup>27</sup> Other antivirals may be effective but efficacy has not been proven in clinical trials.

## Counselling

- Diagnosis often causes considerable distress<sup>25</sup>. Most people with recurrences adjust over time but antiviral treatment can probably reduce anxiety, assist adjustment and improve quality of life<sup>28, 29</sup> (II, B).
- Counselling should be as practical as possible and address particular personal situations; issues for someone in a long-term relationship are likely to be different from those for someone seeking a partner.
- Disclosure is often a difficult issue for patients but is more likely to happen in the context of an on-going relationship<sup>29a</sup>.
- Failure by the patient to control everyday stresses does not affect recurrences.
- For most patients one or two counselling sessions with an invitation to return in case of difficulty should be enough.
- Patients who have failed to adjust to the diagnosis after a year should be considered for more intensive counselling interventions.
- Counselling should cover:
  - Natural history
  - The use of antiviral drugs for symptom control; current uncertainties about impact on infectivity should be discussed
  - Discussion of the risks of transmission by sexual contact related to the actual situation of the patient.
  - Reassurance regarding transmission by fomites and autoinoculation after the first infection is over.
  - Abstinence from sexual contact during lesional recurrences or prodromes.
  - Transmission may occur as a result of asymptomatic viral shedding.
  - Seropositive patients with unrecognised recurrences can be taught to recognise symptomatic episodes after counselling and this may prevent onward transmission<sup>30, 31, 32</sup>.
  - The possible benefit of condoms in reducing transmission, emphasizing that their use cannot completely prevent transmission.
  - Pregnancy issues for both men and women (see below)

## Patient Support

- The distressing nature of symptoms and the stigma associated with HSV infection, as with other conditions <sup>32a</sup>, often results in impaired patient retention of information given by clinical staff.
- The Family Planning Association (fPA) produces a range of leaflets on sexual health for the NHS. Their leaflet on genital herpes provides comprehensive patient information based on BASHH guidelines and be purchased or viewed as a non-printable pdf file on-line.  
[www.fpa.org.uk/attachments/published/144/PDF%20Genital%20herpes%20October%202006.pdf](http://www.fpa.org.uk/attachments/published/144/PDF%20Genital%20herpes%20October%202006.pdf)
- Patients frequently benefit from talking to the Herpes Viruses Association helpline 0845 123 2305 - weekdays.  
Office phone line to order patient materials 020 7607 9661;  
Email: [info@herpes.org.uk](mailto:info@herpes.org.uk)  
Website: [www.herpes.org.uk](http://www.herpes.org.uk)
- Another useful website for patient information is provided by the International Herpes Alliance: [www.herpesalliance.org](http://www.herpesalliance.org)

### **Partner notification**

- Is an effective way of detecting individuals with unrecognised disease <sup>33</sup>
- May clarify whether a partner is infected or not (utilising type-specific antibody testing if necessary). This may help to relieve anxiety about transmission or reinforce the need to reduce the risk of transmission
- May help with the counselling process
- Awareness of the diagnosis in a partner or ex-partner may prevent further onward transmission.

### **Herpes vaccines**

There are no vaccines currently approved for prevention of genital herpes although trials are ongoing. Published studies <sup>35,36</sup> using the HSV-2 glycoprotein-D adjuvant vaccine have shown limited efficacy in preventing clinical disease and only in women who were seronegative for both HSV-1 and HSV-2 at baseline. We do not support the use of unauthorized or unlicensed vaccines outside of clinical trials.

### **Management of herpes in pregnancy**

Guidelines for GH in pregnancy are categorised into management of first episodes and recurrent episodes. Accurate clinical classification is difficult <sup>37</sup>. Viral isolation and typing and the testing of paired sera (if a booking specimen is available) may be helpful. Referral to a Genitourinary Physician for advice on management of women with suspected genital herpes is recommended.

A large prospective study involving 58,000 women in the USA found 202 in whom HSV was isolated at the time of labour <sup>50</sup>. There were 10 cases of neonatal herpes. Risk factors for neonatal herpes were first episode genital herpes, HSV-1 isolation, invasive monitoring, delivery before 38 weeks gestation, and maternal age less than 21 years. Neonatal HSV infection rates per 100 000 live births were 54 (95% CI, 19.8-118) among HSV-seronegative women, 26

(95% CI, 9.3-56) among women who were HSV-1 seropositive only, and 22 (95% CI, 4.4-64) among all HSV-2 seropositive women.

### **First Episode genital herpes**

#### First and second trimester acquisition

- First episode genital herpes has been associated with first trimester miscarriage however there is no conclusive evidence that it causes developmental abnormality if the pregnancy continues. The occurrence of FEGH is not considered an indication for termination of pregnancy. An anomaly scan may be considered at 20-22 weeks gestation where this is not routine.
- Management should be in line with the clinical condition with the use of either oral or intravenous aciclovir.
- Although aciclovir is not licensed for use in pregnancy, there is substantial clinical experience supporting its safety<sup>51</sup>.
- Vaginal delivery should be anticipated (IV, C).
- Daily suppressive aciclovir from 36 weeks gestation<sup>40-46</sup> may be considered for women who experience a first-episode of genital herpes in order to reduce the likelihood of HSV lesions at term, and the offer of Caesarean section (CS) delivery (1b, B). There are sound arguments for using aciclovir 400mg tid because of the altered pharmacokinetics of the drug in late pregnancy.

#### Third trimester acquisition (IV, C)

- CS for the prevention of neonatal herpes has not been evaluated in randomised controlled trials.
- Caesarean section should be offered to all women presenting with first-episode genital herpes lesions at the time of delivery, or within 6 weeks of the expected date of delivery or onset of labour. However Caesarean section may not be of benefit in reducing transmission for women presenting with ruptured membranes for greater than four hours. In all these cases the paediatricians should be informed (B).
- Continuous aciclovir in the last 4 weeks of pregnancy reduces the risk of both clinical recurrence at term and delivery by Caesarean section (CS) (1b, B)<sup>40</sup>.
- If vaginal delivery is unavoidable or where the mother opts for a vaginal birth, prolonged rupture of membranes should be avoided and invasive procedures should not be used. IV aciclovir given intrapartum to the mother and subsequently to the neonate may be considered. The paediatricians should be informed.

### **Recurrent Genital Herpes (III, B)**

- Antiviral treatment is rarely indicated for treatment of recurrent episodes of genital herpes during pregnancy.
- Symptomatic recurrences during the third trimester are likely to be brief; vaginal delivery is appropriate if no lesions are present at delivery.

- If there are no genital lesions at delivery, CS to prevent neonatal herpes should not be performed.
- Cultures during late gestation to predict viral shedding at term are not indicated.
- Sequential cultures during late pregnancy do not predict viral shedding at term<sup>39</sup>.
- The benefits of obtaining specimens for culture at delivery to identify women who are asymptotically shedding HSV are unproven.
- Aciclovir suppressive treatment from 36 weeks gestation may be considered.
- A systematic review<sup>40</sup> of five randomised clinical trials<sup>41-46</sup> involving a total enrolment of 799 patients has shown that aciclovir prophylaxis beginning at 36 weeks gestation was effective in reducing clinical HSV recurrences at the time of delivery (OR 0.25; 95% confidence interval 0.15, 0.40), reducing CS deliveries for clinical recurrence of genital herpes (OR 0.30; 95% CI 0.13, 0.67), reducing total HSV detection at delivery (OR 0.11; 95% CI 0.04, 0.31), and asymptomatic shedding at delivery (OR 0.09; 95% CI 0.02, 0.39). (Evidence level IA, A).
- The use of aciclovir prophylaxis may also be cost-effective<sup>47</sup>.
- Two randomized controlled trials of valaciclovir prophylaxis to prevent recurrent genital herpes at term were reported in 2006. The first<sup>47b</sup> involved a total of 112 enrolled patients who were HSV-2 seropositive. Valaciclovir use in comparison with placebo reduced the number of women with clinical recurrences between the time of randomization and delivery (RR 0.40, 95% CI 0.2, 0.9). However, the proportions of women with viral shedding within 7 days of delivery (10.4% vs 12.0%) and with clinical HSV lesions at delivery (5.3% vs 14.6%) were not statistically different. The second larger study<sup>47c</sup> enrolled a total of 350 women with a history of genital herpes, of whom 82 percent had recurrent genital herpes. The use of valaciclovir as compared with placebo was associated with a significantly reduced proportion of women requiring CS delivery (4% vs 13%, p=0.009), and with positive HSV cultures (2% vs 9%, p<0.02)

### **Genital lesions at the onset of labour (III, B)**

- Caesarean section should be considered for women with recurrent genital herpes lesions at the onset of labour. Recurrent genital herpes at any other time during pregnancy is not an indication for delivery by Caesarean section. The risks of vaginal delivery for the fetus are small and must be set against risks to the mother of CS<sup>48</sup>.
- Clinical diagnosis of genital herpes at the time of labour correlates relatively poorly with HSV detection from genital sites or lesions by culture or PCR and fails to identify asymptomatic women who have HSV in their genital secretions at the time of labor. Thus, the presence of genital lesions has a sensitivity for HSV detection of 37% by culture and 41% by PCR<sup>49</sup>.
- For women with a history of recurrent genital herpes, who would opt for Caesarean delivery if HSV lesions were to be detected at the onset of labour, daily suppressive aciclovir given from 36 weeks gestation until delivery may be given to reduce the likelihood of HSV lesions at term (A).

### **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<sup>52,53</sup>.
- Women may be asked about or may volunteer at their first antenatal visit a history that they or their male partner have had genital herpes.
- Women who report a history of genital herpes can be reassured that the risk of transmission to the neonate is very small, even if genital lesions are present at delivery.
- Recurrences during pregnancy pose no threat to the pregnancy or well-being of the foetus.
- Identifying women susceptible to acquiring genital herpes in pregnancy by means of type-specific screening for HSV antibodies in pregnancy has not been shown to be cost-effective and is not currently indicated in the UK.
- Female partners of men with genital herpes, who themselves give no history of genital herpes, should be advised about reducing their risk of acquiring this infection. Women may reduce their risk of acquiring herpes during pregnancy and of subsequent transmission to the neonate by using condoms consistently, especially the third trimester, and abstaining from sexual intercourse during recurrences. Women should avoid receptive oro-genital contact if their partner has oro-labial herpes.
- All women, not just those with a history of GH, should undergo careful vulval inspection at the onset of labour to look for clinical signs of Herpes simplex infection.
- Neonatal herpes may occur as a result of nosocomial or community-acquired infection<sup>54,55</sup>. Mothers, staff, and other relatives/friends with active HSV infection, such as orolabial herpes or herpetic whitlow, should avoid direct contact between lesions and the neonate.

## Management of genital herpes in people with HIV

- There is epidemiological synergy between Herpes simplex virus (HSV) and HIV infections<sup>56,57</sup>. Herpes simplex infections activate HIV replication<sup>58-62</sup> and may facilitate onward HIV transmission to sexual partners<sup>63-65</sup>. Suppressive treatment of HSV-2 infection with valaciclovir has been shown to reduce genital HIV shedding in women<sup>66</sup>. In addition, both prevalent and incident HSV 2 infections are associated with an increased risk of HIV acquisition<sup>67,68</sup>.
- Genital herpes is the most common STI in HIV positive heterosexuals in the UK<sup>69</sup>. 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<sup>70-72</sup>.
- Standard systemic antiviral drugs, as used to treat genital herpes in HIV-uninfected patients, have been shown to successfully treat genital herpes PWHIV<sup>73-78</sup>. Resistance to antiherpes drugs is more common in those with HIV co-infection and is associated with treatment failure of genital herpes<sup>79</sup>.
- 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<sup>80-84</sup>. HSV associated IRIS may be unresponsive to previously effective anti-herpes viral therapy in the absence of increased antiviral resistance. Management is difficult but topical cidofovir may be effective.

### First episode genital herpes

- In the absence of HIV therapy, primary genital herpes may be severe and prolonged with risk of progressive, multifocal and coalescing mucocutaneous anogenital lesions. Moreover, serious and potentially life-threatening systemic complications, such as fulminant hepatitis, pneumonia, neurological disease and disseminated infection have been reported.
- Prompt initiation of therapy is recommended if herpes is suspected clinically. If new lesions are still forming after 3-5 days, a repeat viral culture with susceptibility testing should be performed and the dose of HSV therapy increased. Definitive studies in PWHIV are lacking.
  - Recommended regimens<sup>86</sup>. (Evidence level IIb, B)
    - Aciclovir 400 mg five times daily for 7-10 days.
    - Valaciclovir 1 gram twice daily for 10 days
    - Famciclovir 250-750 mg twice daily for 10 days

- In severe cases, initiation of therapy with aciclovir 5-10 mg/kg body weight IV every 8 hours may be necessary. Induction therapy should be continued intravenously for 2-7 days, or until clinical improvement, and followed by oral antiviral therapy to complete a minimum of 10 days total treatment. (Evidence level IV, C).

### **Recurrent Genital Herpes**

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

### **Episodic Treatment**

In controlled trials in HSV and HIV co-infected persons, episodic treatment with the following regimens was found to be effective<sup>87-89</sup>.

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

The following drug regimens are recommended for episodic treatment (Evidence level IV, C)<sup>86</sup>

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

### **Suppressive Treatment**

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

Recommended drug regimens for daily suppressive treatment<sup>86,90-91</sup>

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

- Valaciclovir 500 mg orally twice a day

### **Drug resistant genital herpes**

- In prospective studies, aciclovir-resistant strains have been found in around 5-7% isolates from genital herpes lesions in HIV-infected persons<sup>92-94</sup>. 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<sup>95-96</sup>. 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<sup>95-97</sup>. TK-deficient strains are susceptible to foscarnet and cidofovir which do not depend upon TK but which inhibit viral DNA polymerase.
- Antiviral susceptibility testing for HSV is not currently available in the UK. Clinical response to antiviral therapy is used to guide decisions, Advice from a clinical virologist about appropriate drug dosages and duration may be sought when clinical resistance is suspected.
- Both topical 1% foscarnet cream<sup>98</sup> and 1% cidofovir gel<sup>99</sup> have been shown to produce significant benefits in lesion healing, pain reduction and virological effect in drug resistant herpes in PWHIV. (Evidence level Ib, A).
- There is limited evidence to support the use of topical trifluorothymidine alone or in combination with interferon-alpha<sup>100,101</sup> (Evidence level IIb, B).
- Systemic therapy with either foscarnet or cidofovir is generally preferred to treat drug resistant herpes in those with HIV. There is evidence for:
  - Foscarnet 40 mg/kg body weight IV every 8 hours until clinical resolution<sup>102-103</sup>. (Evidence level Ib, A).
  - Cidofovir 5mg/kg body weight weekly IV infusion<sup>104-107</sup> (Evidence level IV)
- Cidofovir is administered with oral probenecid and adequate pre-hydration to reduce the risk of nephrotoxicity. It may be effective in aciclovir-resistant infections that are also resistant to foscarnet. Initial therapy at 5mg/kg is given weekly, as an infusion over one hour, for two weeks. Systemic treatment should continue until clinical resolution is attained.
- Alternating courses of treatment with aciclovir and cidofovir for subsequent recurrences has been advocated as a strategy that may reduce the development of cidofovir-resistant strains. The efficacy, safety, and durability

of the therapeutic response of these agents have yet to be determined in prospective controlled trials.

The relative costs of antivirals are given in table 2

### **Auditable outcome measures**

- Virological confirmation should be attempted in all patients. Target 100%.
- At least one viral isolate should be typed. Target 100%.
- Patients presenting early in the course of first episode GH should be offered antiviral therapy. Target 100%.
- Patients with a diagnosis of GH should be offered counselling, support, and written information. Target 100%.
- Suppressive therapy should be offered to all patients with more than six recurrences annually. Target 100%.
- If suppressive therapy is commenced, a clear plan of duration of treatment should be entered in the notes and the patient should be reviewed in accordance with this. Target 100%.

### **Authors**

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

### **Membership of the CEG**

Dr Keith Radcliffe (Chair), Whittall Street Clinic, Birmingham (BASHH)

Dr Imtyaz Ahmed-Jushuf, Nottingham City Hospital (BASHH)

Dr David Daniels, West Middlesex Hospital (Chair, NAG)

Dr Mark FitzGerald, Taunton & Somerset (BASHH)

Dr Gill McCarthy, Kingston Hospital (BASHH)

Dr Neil Lazaro (RCGP)

Dr Guy Rooney, Swindon & Oxford (RCP)

### **Conflict of interest**

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

Table 1 Positive predictive values for HSV-2 antibody assays

	<b>Prevalence</b>	<b>Positive predictive value*</b>
Sexually transmitted infection clinic <sup>9</sup>	25%	86%
General population antenatal clinic <sup>11</sup>	5%	50%

\*(for an assay with 95% sensitivity and specificity)

Table 2 Relative costs of antiviral drugs for treating genital herpes\*

<b>Indication</b>	<b>Treatment duration</b>	<b>Aciclovir</b>	<b>Famciclovir</b>	<b>Valaciclovir</b>
<b>First episode</b>	5 days	£4.01	£92.79	£21.86
<b>Recurrence</b>	5 days	£4.01	£30.93	£21.86
<b>Suppression</b>	1 year	£95.03	£4503.07	£419.94

\*Source of costing DMG tariff BNF September 2005 (Different prices may be negotiated by NHS hospital trusts).

## References:

1. Langenberg AG, Corey L, Ashley RL, *et al*. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV Vaccine Study Group. *N Engl J Med* 1999; **341**: 1432-8.
2. Scoular A *et al*, Longitudinal study of genital infection by herpes simplex virus type 1 in western Scotland over 15 years. *BMJ* 2002; **324**: 1366-1367
- 2A. Geretti A M. Genital Herpes. *Sex Transm. Infect.* 2006;82:31-34
3. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first episode infection. *Ann Intern Med* 1994;**121**:847-54.
4. Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med* 1999; **131**: 14-20.
5. Wald A, Zeh J, Selke S, *et al*. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 2000; **342**: 844-50.
6. Krone MR, Wald A, Tabet SR, *et al*. Herpes simplex virus type 2 shedding in human immunodeficiency virus-negative men who have sex with men; frequency, patterns and risk factors. *Clinical Infectious Diseases* 2000; **30**: 261-7.
7. Schacker T, Zeh J, Hu HL, *et al*. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men . *J Infect Dis* 1998; **178**: 1616-22.
- 7A Scoular A. Using the evidence base on genital herpes:optimizing the use of diagnostic tests and information provision. *Sex Transm.Infect* 2002; **78**:160-165
- 8.Geretti AM, Brown WD. National survey of diagnostic services for genital herpes. *Sex Transm Infect.* 2005;**81**:316-7.
9. Scoular A. Using the evidence base on genital herpes: optimising the use of diagnostic tests and information provision. *Sex Transm Infect* 2002;**78**:160-5.
- 10.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.
- 11.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**:406-410.
- 12.Ashley RL. Performance and use of HSV type-specific serology test kits. *Herpes* 2002;**9**:38-45.
13. 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.
14. <http://www.herpeselect.com> (accessed February 2006).  
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.
15. Corey L, Benedetti J, Critchlow C, *et al*. Treatment of primary first-episode genital herpes simplex virus infections with acyclovir: results of topical, intravenous and oral therapy.

*J Antimicrob Chemother* 1983;**12**(Suppl B):79-88.

16. Fife KH, Barbarash RA, Rudolph T, *et al.* Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection. Results of an international, multicenter, doubleblind, randomised clinical trial. The Valaciclovir International Herpes Simplex Virus Study Group. *Sex Transm Dis* 1997;**24**:481-6.

17. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR—Recommendations and Reports*. 2002; **51**(RR-6).

18. Corey L, Mindel A, Fife KH, *et al.* Risk of recurrence after treatment of first-episode genital herpes with intravenous acyclovir. *Sex Transm Dis* 1985;**12**:215-8.

19. Nilsen AE, Aasen T, Halos AM, *et al.* Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet* 1982;ii:571-3.

20. Spruance SL, Tyring SK, DeGregoria B, *et al.* and the Valaciclovir study group. A largescale, placebo controlled, dose ranging trial of peroral valaciclovir for episodic treatment of recurrent herpes genitalis. *Arch Intern Med* 1996;**156**:1729-35.

21. Sacks SL, Aoki FY, Diaz-Mitoma F, *et al.* 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.

21a. Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis*. 2002 Apr 1;**34**(7):944-8. Epub 2002 Feb 20

21b. 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 Jan 1;**42**(1):8-13. Epub 2005 Nov 23.

21c. 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 Apr 1;**34**(7):958-62. Epub 2002 Feb

21d. Strand A, Patel R, Wulf HC, Coates KM; International Valaciclovir HSV Study Group. Aborted genital herpes simplex virus lesions: findings from a randomised controlled trial with valaciclovir. *Sex Transm Infect*. 2002 Dec;**78**(6):435-9

22. Patel R, Bodsworth NJ, Woolley P, *et al.* and the International Valaciclovir HSV Study Group. Valaciclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once daily therapy. *Genitourinary Medicine* 1997;**73**:105-9.

23. Mertz GJ, Loveless MO, Levin MJ, *et al.* Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women. A multicenter, double-blind, placebocontrolled trial. Collaborative Famciclovir Genital Herpes Research Group. *Arch Intern Med* 1997;**157**:343-9.

24. Girard M. Safety of acyclovir in general practice: a review of the literature. *Pharmacoepidemiology and Drug Safety* .1996; **5**: 325-332.

25. Wald A, Zeh J, Barnum G, *et al.* Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. *Ann Intern Med* 1996;**124**:8-15.

26. Jungmann EM. Genital Herpes. *Clin Evid Concise* 2004;**11**:390-3

- 26b Wald A, Selke S, Warren T, Aoki FY, Sacks S, Diaz-Mitoma F, Corey L.  
Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding.  
*Sex Transm Dis.* 2006 Sep;33(9):529-33
- 26c Gupta R, Wald A, Krantz E, Selke S, Warren T, Vargas-Cortes M, Miller G, Corey L.  
Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract.  
*J Infect Dis.* 2004 Oct 15;190(8):1374-81. Epub 2004 Sep 20..
27. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *New England Journal of Medicine* 2004;350(1):11-20.
28. Green J, Kocsis A. Psychological factors in recurrent genital herpes. *GenitourinaryMedicine*, 1997; 73: 253-259.
29. Patel R, Tying 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
30. Mertz GJ, Benedetti J, Ashley R, et al. Risk factors for the sexual transmission of genital herpes. *Ann Intern Med* 1992;116:197-202.
31. Carney O, Holder MA, Ikkos G, et al. The effect of suppressive oral aciclovir on the psychological morbidity associated with recurrent genital herpes. *Genitourinary Medicine* 1993; 69: 457-9.
32. Langenberg A, Benedetti J, Jenkins J, et al. Development of clinically recognizable genital lesions among women previously identified as having 'asymptomatic' herpes simplex virus type 2 infection. *Ann Intern Med* 1989;110:882-7
- 32a. Kessels RPC. Patients' memory for medical information. *J R Soc Med* 2003;96: 219-22
33. Mertz GJ, Schmidt O, Jourdan JL, et al. Frequency of acquisition of first episode genital infection with herpes simplex virus infection from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985; 12:33-9.
35. Stanberry LR, Spruance SL, Cunningham AL, et al. Glycoprotein-D-Adjuvant vaccine to prevent genital herpes. *N Engl J Med.* 2002;347(21):1652–1661.
36. Corey L, Langenberg AG, Ashley R, et al. Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection. *JAMA.* 1999;282(4): 331–340.
37. Hensleigh PA, Andrews WW, Brown Z et al. Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. *Obstet Gynecol* 1997; 89: 891-5.
38. Scott LL, Sanchez PJ, Jackson GL, et al. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. *Obstet Gynecol* 1996; 87: 69-73.

39. Prober CG, Hensleigh PA, Boucher FD, *et al.* Use of routine viral cultures at delivery to identify neonates exposed to herpes simplex virus.  
*N Engl J Med* 1988; **318** :887-91.
40. 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.
41. 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.
- 42 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.
43. 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.
44. 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.
46. 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.
47. Randolph AG, Hartshorn RM, Washington AE. Acyclovir prophylaxis in late pregnancy to prevent neonatal herpes: a cost-effectiveness analysis.  
*Obstet Gynecol* 1996; **88**: 603-10.
- 47b. 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
- 47c. 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
48. Prober CG, Sullender WM, Yasukawa LL, *et al.* Low risk of herpes simplex virus infections in neonates exposed to the virus at the time of vaginal delivery to mothers with recurrent genital herpes.  
*N Engl J Med* 1987; **316**: 240-4.
49. 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
50. Brown ZA, Wald A, Ashley Morrow R, Selke S, Zeh J, Corey L  
Effect of Serologic Status and Cesarean Delivery on Transmission Rates of Herpes Simplex Virus From Mother to Infant.  
*JAMA.* 2003;**289**:203-209.
51. Acyclovir and Valacyclovir in Pregnancy Registry final report. April 1999. Available at:

<http://pregnancyregistry.gsk.com/acyclovir.html>.

52. Vonau B, Low-Beer N, Barton SE, Smith JR. Antenatal serum screening for genital herpes: a study of knowledge and attitudes of women at a central London hospital [see comments]. *Br J Obstet Gynaecol* 1997;**104**:347–9.

53. Cleary KL, Pare E, Stamilio, et al. Type-specific screening for symptomatic herpes infection in pregnancy: a decision analysis. *BJOG* 2005; **112**: 731-6

54. Douglas J, Schmidt O, Corey L. Acquisition of neonatal HSV-1 infection from a paternal source contact. *J Pediatr* 1983;**103**:908–10.

55. Hammerberg O, Watts J, Chernesky M, Luchsinger I, Rawls W. An outbreak of Herpes simplex virus type 1 in an intensive care nursery. *Pediatr Infect Dis* 1983;**2**:290–4

56. Wasserheit JN. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis* 1992;**19**: 61–77.

57. Hook EW, III, Cannon RO, Nahmias AJ, Lee FF, Campbell CH, Glasser D et al. Herpes simplex virus infection as a risk factor for human immunodeficiency virus in heterosexuals. *J Infect Dis* 1992;**165**:251–255.

58. Mosca JD, Bednarik DP, Raj NBK, Rosen CA, Sodroski JG, Haseltine WA et al. Activation of human immunodeficiency virus by herpesvirus infection: identification of a region within the long terminal repeat that responds to a trans-acting factor encoded by herpes simplex virus 1. *Proc Natl Acad Sci U S A* 1987;**84**:7408–7412.

59. Ostrove JM, Leonard J, Weck KE, Rabson AB, Gendelman HE. Activation of the human immunodeficiency virus by herpes simplex type 1. *J Virol* 1987;**61**:3726–3372.

60. Golden MP, Kim S, Hammer SM, Ladd EA, Schaffer PA, DeLuca N et al. Activation of human immunodeficiency virus by herpes simplex virus. *J Infect Dis* 1992;**166**:494–499.

61. Margolis DM, Rabson AB, Straus SE, Ostrove JM. Transactivation of the HIV-1 LTR by HSV-1 immediate-early genes. *Virology* 1992; **186**:788–791.

62. Koelle DM, Abbo H, Peck A, Ziegweid K, Corey L. Direct recovery of herpes simplex virus (HSV)-specific T lymphocyte clones from recurrent genital HSV-2 lesions. *J Infect Dis* 1994; **169**:956–961.

63. Kreiss J, Carael M, Meheus A. Role of sexually transmitted diseases in transmitting human immunodeficiency virus. *Genitourin Med* 1988; **64**:1–2.

64. Kreiss JK, Coombs R, Plummer F, Holmes KK, Nikora B, Cameron W et al. Isolation of human immuno-deficiency virus from genital ulcers in Nairobi prostitutes. *J Infect Dis* 1989;**160**:380–384.

65. Schacker T, Ryncarz AJ, Goddard J, Diem K, Shaughnessy M, Corey L. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. *JAMA* 1998;**280**:61–66.

66. Nagot N, Ouedraogo A, Mayaud P, Konate I, Vergne L, Weiss H, Foulongne V, Djagbare D, Segongy M, Vande Perre P and ANRS 1285 Study Group. Effect of HSV-2 Suppressive Therapy on HIV-1 Genital Shedding and Plasma Viral Load: A Proof of Concept Randomized Double-Blind

Placebo Controlled Trial (ANRS 1285 Trial). Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 33LB, 2006.

67. Todd J, Grosskurth H, Changalucha J, Obasi A, Mosha F, Balira R, Orroth K, Hugonnet S, Pujades M, Ross D, Gavyole A, Mabey D, Hayes R. Risk Factors Influencing HIV Infection Incidence in a Rural African Population: A Nested Case-Control Study. *J Infect Dis.* 2006 Feb **1**;193(3):458-66.
68. Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS.* 2006 Jan 2;**20**(1):73-83.
69. O'Farrell N, Tovey SJ. High cumulative incidence of genital herpes amongst HIV-1 seropositive heterosexuals in south London. *Int J STD AIDS.* 1994 Nov-Dec;**5**(6):415-8.
70. Chen CY, Ballard RC, Beck-Sague CM, Dangor Y, Radebe F, Schmid S et al. Human immunodeficiency virus infection and genital ulcer disease in South Africa: the herpetic connection. *Sex Transm Dis* 2000;**27**:21-29.
71. Bagdades EK, Pillay D, Squire SB, O'Neil C, Johnson MA, Griffiths PD. Relationship between herpes simplex virus ulceration and CD4+ cell counts in patients with HIV infection. *AIDS* 1992;**6**: 1317-1320.
72. Wright PW, Hoesley CJ, Squires KE, Croom-Rivers A, Weiss HL, Gnann JW Jr. A prospective study of genital herpes simplex virus type 2 infection in human immunodeficiency virus type 1 (HIV-1)-seropositive women: correlations with CD4 cell count and plasma HIV-1 RNA level. *Clin Infect Dis* 2003;**36**:207-11.
73. Quinnan GV, Masur H, Rook AH, Armstrong G, Frederick WR, Epstein J et al. Herpes-virus infections in the acquired immune deficiency syndrome. *JAMA* 1984;**252**: 72-77.
74. Maier JA, Bergman A, Ross MG. Acquired immuno-deficiency syndrome manifested by chronic primary genital herpes. *Am J Obstet Gynecol* 1986; **155**:756-758.
75. Leung DT, Sacks SL. Current recommendations for the treatment of genital herpes. *Drugs* 2000;**60**:1329-1362.
76. Drew WL, Stempien MJ, Kheraj M, Erlich KS. Management of herpesvirus infections (cytomegalovirus, herpes simplex virus and varicella-zoster virus). In: *The Medical Management of AIDS*, 6th edn (Sande MA, Volberding PA, eds). Philadelphia: WB Saunders, 1999; 444.
77. Aoki FY. Management of genital herpes in HIV-infected patients. *Herpes* 2001;**8**:41-45.
78. Foley E, Patel R. Treatment of genital herpes in HIV-infected patients. *Journal of HIV Therapy* 2004;**9**:14-18.
79. Marks G, Nolan P, Erlich K, Ellis M. Mucocutaneous dissemination of acyclovir-resistant herpes simplex virus in a patient with AIDS. *Rev Infect Dis* 1989;**2**:474-476.
80. Sacks SL, Wanklin RJ, Reece DE, Hicks KA, Tyler KL, Coen DM. Progressive esophagitis from acyclovir-resistant herpes simplex. Clinical roles for DNA polymerase mutants and viral heterogeneity? *Ann Intern Med* 1989;**111**:893-899.
81. Gateley A, Gander R, Johnson P, Kit S, Otsuka H, Kohl S. Herpes simplex virus type 2 meningoencephalitis resistant to acyclovir in a patient with AIDS. *J Infect Dis* 1990;**161**: 711-715.

82. Englund JA, Zimmerman ME, Swierkosz EM, Goodman JL, Scholl DR, Balfour HH Jr. Herpes simplex virus resistant to acyclovir. A study in a tertiary care center. *Ann Intern Med*. 1990 Mar 15; **112**(6):416-22.
83. Ratnam I, Chiu C, Kandala N-B, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV Type 1-infected cohort. *Clin Infect Dis* 2006; **42**: 418-427.
84. Fox PA, Barton SE, Francis N, Youle M, Henderson DC, Pillay D, Johnson MA, Fearfield L, Gazzard BG, Bunker CB. Chronic erosive herpes simplex virus infection of the penis, a possible immune reconstitution disease. *HIV Med*. 1999 Oct; **1**(1):10-8.
85. French MA, Lenzo N, John M, Mallal SA, McKinnon EJ, James IR, Price P, Flexman, JP, Tay-Kearney ML. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med*. 2000 Mar; **1**(2):107-15.
86. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR Recomm Rep* 2002 May 10; **51**(RR-6):1-78.
87. Leone PA, Trottier S, Miller JM. Valacyclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. *Clin Infect Dis*. 2002 Apr 1; **34**(7):958-62.
88. 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.
89. Schacker T, the International Valaciclovir HSV Study Group. Valaciclovir as acute treatment for recurrent anogenital herpes in immuno-compromised (HIV positive) individuals (abstract). International Society for Sexually Transmitted Diseases Research (ISSTD), Denver, USA, 1999.
90. DeJesus E, Wald A, Warren T, Schacker TW, Trottier S, Shahmanesh M, Hill JL, Brennan CA; Valacyclovir International HSV Study Group. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. *J Infect Dis*. 2003 Oct 1; **188**(7):1009-16
91. Warren T, Harris J, Brennan CA. Efficacy and safety of valacyclovir for the suppression and episodic treatment of herpes simplex virus in patients with HIV. *Clin Infect Dis*. 2004 Nov 1; **39** Suppl 5:S258-66.
92. Reyes M, Shaik NS, Graber JM, Nisenbaum R, Wetherall NT, Fukuda K, Reeves WC; Task Force on Herpes Simplex Virus Resistance. Acyclovir-resistant genital herpes among persons attending sexually transmitted disease and human immunodeficiency virus clinics. *Arch Intern Med*. 2003 Jan 13; **163**(1):76-80.
93. Stranska R, Schuurman R, Nienhuis E, Goedegebuure IW, Polman M, Weel JF, Wertheim-Van Dillen PM, Berkhout RJ, van Loon AM. Survey of acyclovir-resistant herpes simplex virus in the Netherlands: prevalence and characterization. *J Clin Virol*. 2005 Jan; **32**(1):7-18.
94. Hill EL, Hunter GA, Ellis MN. In vitro and in vivo characterization of herpes simplex virus clinical isolates recovered from patients infected with human immunodeficiency virus. *Antimicrob Agents Chemother* 1991; **35**: 2322–2328.
95. Safrin S. Treatment of acyclovir-resistant herpes simplex virus infections in patients with AIDS. *J Acquir Immune Defic Syndr* 1992; **5**(Suppl 1):S29–S32.

96. Gnann JW, Davis MG, Harden EA, Kern ER, Task Force on HSV Resistance. Acyclovir-resistant HSV from HIV-infected individuals. Population surveillance and in vitro characterization of isolates (abstract). 38<sup>th</sup> Annual International Disease Society of America (IDSA) Meeting, New Orleans, USA, 2000.
97. Engel JP, Englund JA, Fletcher CV, Hill EL. Treatment of resistant herpes simplex virus with continuous-infusion acyclovir. *JAMA* 1990;**263**: 1662–1664.
98. Javalay K, Wohlfeiler M, Kalayjian R, Klein T, Bryson Y, Grafford K et al. Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. *J Acquir Immune Defic Syndr* 1999;**21**: 301–306.
99. Lalezari J, Schacker T, Feinberg J, Gathe J, Lee S, Cheung T et al. A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Infect Dis* 1997;**176**:892–898.
100. Birch CJ, Tyssen DP, Tachedjian G, Doherty R, Hayes K, Mijch A et al. Clinical effects and in vitro studies of trifluorothymidine combined with interferon- $\alpha$  for treatment of drug-resistant and -sensitive herpes simplex virus infections. *J Infect Dis* 1992;**166**:108–112.
101. Kessler HA, Hurwitz S, Farthing C, Benson CA, Feinberg J, Kuritzkes DR et al. Pilot study of topical tri-fluridine for the treatment of acyclovir-resistant mucocutaneous herpes simplex disease in patients with AIDS (ACTG 172). *J Acquir Immune Defic Syndr* 1996;**12**:147–152.
102. Safrin S, Crumpacker C, Chatis P, Davis R, Hafner R, Rush J et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. *N Engl J Med* 1991;**325**:551–555.
103. Bestman-Smith J, Boivin G. Herpes simplex virus isolates with reduced adefovir susceptibility selected in vivo by foscarnet therapy. *J Med Virol* 2002 ;**67**:88-91.
104. LoPresti AE, Levine JF, Munk GB, Tai CY, Mendel DB. Successful treatment of an aciclovir- and foscarnet-resistant herpes simplex virus type 1 lesion with intravenous cidofovir. *Clin Infect Dis* 1998; **26**: 512-3
105. Snoek R. Antiviral therapy of herpes simplex. *Int J Antimicrob Agents* 2000; **16**: 157-9.
106. Morfin F, Thouvenot D. Herpes simplex virus resistance to antiviral drugs. *J Clin Virol* 2003; **26**:29-37.int-Leger E, Fillet AM, Malvy D, Rabanel B, Caumes E. Efficacy of cidofovir in an HIV infected patient with an aciclovir and foscarnet resistant herpes simplex virus infection. *Ann Dermatol Venereol* 2001; **128**: 747-9
- 107.Kopp T, Geusau A, Rieger A, Stingl G. Successful treatment of an aciclovir-resistant herpes simplex type 2 infection with cidofovir in an AIDS patient. *Br J Dermatol* 2002; **147**: 134-8