**ABSTRACT**

**INTRODUCTION:** Genital herpes is an infection with herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2), and is among the most common sexually transmitted diseases. **METHODOLOGY AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent sexual transmission of herpes simplex virus? What are the effects of interventions to prevent transmission of herpes simplex virus from mother to neonate? What are the effects of antiviral treatment in people with a first episode of genital herpes? What are the effects of interventions to reduce the impact of recurrence? What are the effects of treatments in people with genital herpes and HIV? We searched Medline, Embase, The Cochrane Library, and other important databases up to January 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 35 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review we present information relating to the effectiveness and safety of the following interventions: antivirals, caesarean delivery, condoms, oral aciclovir, psychotherapy, recombinant glycoprotein vaccines, serological screening, and counselling.

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### QUESTIONS

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### INTERVENTIONS

#### PREVENTING SEXUAL TRANSMISSION

- **Likely to be beneficial**
  - Antiviral treatment of infected sexual partner with valaciclovir (reduced transmission to uninfected partner) 4
  - Male condom use to prevent sexual transmission from infected men to uninfected sexual partners 4
  - Male condom use to prevent sexual transmission from infected women to uninfected men* 5

- **Unknown effectiveness**
  - Female condoms 5
  - Recombinant glycoprotein vaccines (gB2 plus gD2) in people at high risk of infection (no effect except in women known to be HSV-1 and HSV-2 negative before vaccination) 6

- **unlikely to be beneficial**
  - Oral antiviral treatment taken at the start of recurrence 7

#### PREVENTING TRANSMISSION FROM MOTHER TO NEONATE

- **Unknown effectiveness**
  - Caesarean delivery in women with genital lesions at term to prevent neonatal herpes 7
  - Antiviral maintenance treatment (oral) in late pregnancy (at least 36 weeks' gestation) to prevent transmission of infection to neonates from women with a history of genital herpes 7
  - Serological screening and counselling to prevent acquisition of herpes simplex virus in late pregnancy (at least 36 weeks' gestation) 9

#### TREATING FIRST EPISODE

- **Beneficial**
  - Antiviral treatment with oral aciclovir in first episodes of genital herpes 9
  - Different types of oral antiviral treatment for first episodes of genital herpes 10

- **Unknown effectiveness**
  - Daily oral antiviral maintenance treatment in people with high rates of recurrence 10
  - Oral antiviral treatment taken at the start of recurrence 14

#### REDUCING IMPACT OF RECURRENCE

- **Beneficial**
  - Psychotherapy to reduce recurrence 17

#### TREATING PEOPLE WITH HIV

- **Beneficial**
  - Daily oral antiviral treatment for preventing recurrence of genital herpes in people with HIV 17

- **Likely to be beneficial**
  - Antiviral treatment (oral) for first episodes of genital herpes in people with HIV* 19
  - Aciclovir (oral) for an acute recurrent episode of genital herpes in people with HIV (may improve healing rate at 7 days compared with placebo) 20
Genital herpes

Key points

- Genital herpes is an infection with herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2). The typical clinical features include painful shallow anogenital ulceration.
  
  It is among the most common sexually transmitted diseases, with up to 23% of adults in the UK and US having antibodies to HSV-2.

- Genital herpes, like other genital ulcer diseases, is a significant risk factor for acquiring HIV for both men and women. People with HIV can have severe herpes outbreaks, and this may help facilitate transmission of both herpes and HIV infections to others.

- Oral antiviral treatment of someone who is seropositive for HSV seems to be effective in reducing transmission to a previously uninfected partner.

- Despite limited evidence, male condom use is generally believed to reduce sexual transmission of herpes from infected men to uninfected sexual partners.

  We don't know, based specifically on evidence in serodiscordant couples, how effective male condom use is at preventing transmission from infected women to uninfected men. However, based on observational data and clinical experience of the effects of condoms to prevent acquisition of genital herpes in uninfected people, there is consensus that they are likely to be beneficial in preventing transmission from infected women to their uninfected partners.

  We didn't find any evidence examining the effectiveness of female condoms in preventing transmission.

- Recombinant glycoprotein vaccines do not seem any more effective than placebo in preventing transmission to people at high risk from infection.

  We did not find any evidence about other vaccines.

- We found insufficient evidence to draw reliable conclusions on whether antiviral maintenance treatment in late pregnancy, or serological screening and counselling to prevent acquisition of herpes in late pregnancy are effective in preventing transmission of HSV from mother to neonate.

  Caesarean delivery in women with genital lesions at term may reduce the risk of transmission, but is associated with an increased risk of maternal morbidity and mortality.

- Oral antiviral treatments effectively decrease symptoms in people with first episodes of genital herpes, although we found insufficient evidence to establish which type of oral antiviral drug was most effective.

- If herpes is recurrent, aciclovir, famciclovir, and valaciclovir when taken at the start of recurrence are all equally beneficial in reducing duration of symptoms, lesion healing time, and viral shedding.

  Daily maintenance treatment with oral antiviral agents effectively reduces frequency of recurrences, and improves quality of life.

  We don't know whether psychotherapy is effective in reducing recurrence.

- Oral antiviral treatments are likely to be effective in treating recurrent episodes of genital herpes in people with HIV, and are generally believed to be useful in treating first episodes of genital herpes in people with HIV, although evidence supporting this is sparse.

  Oral antiviral treatments are also likely to be effective in preventing recurrence of genital herpes in people with HIV.

DEFINITION

Genital herpes is an infection with herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2). The typical clinical features include painful shallow anogenital ulceration. HSV infections can be confirmed on the basis of virological and serological findings. Using these findings, infections can be categorised as: primary infection, which is defined as HSV confirmed in a person without HSV-1 or HSV-2 antibodies; first episode non-primary infection, which is defined as detection of one viral type in an individual with serological evidence of past infection with the other viral type; and recurrent genital herpes, which is characterised by reactivation of latent HSV-1 or HSV-2 in the presence of antibodies of the same serotype. HSV-1 can also cause gingivostomatitis and orolabial ulcers. HSV-2 can also cause other types of herpes infection, such as ocular herpes. Both virus types can cause infection of the central nervous system (e.g., encephalitis).
## Aims of Intervention
To prevent transmission; to reduce the morbidity of the first episode; to reduce the risk of recurrent disease after a first episode, with minimal adverse effects of treatment.

## Methods
Clinical Evidence search and appraisal January 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2010, Embase 1980 to January 2010, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue).

An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we carried out an observational search for options on male or female condoms to prevent transmission of HSV. We searched for prospective and retrospective cohort studies, population surveillance studies, case-control studies.
and case series. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 24). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

**QUESTION**
What are the effects of interventions to prevent sexual transmission of herpes simplex virus?

**OPTION**
**ANTIVIRAL TREATMENT TO PREVENT SEXUAL TRANSMISSION**

**Transmission of infection**

*Compared with placebo* Daily use of valaciclovir is more effective at reducing the risk of transmission of herpes simplex virus type 2 to a previously uninfected sexual partner at 8 months (moderate-quality evidence).

**For GRADE evaluation of interventions for genital herpes, see table, p 24.**

**Benefits:**
We found no systematic review but we found one RCT (1484 serodiscordant couples).\(^\text{[15]}\) It found that valaciclovir (500 mg once daily, taken by the infected partner) significantly reduced the risk of herpes simplex virus type 2 (HSV-2) transmission compared with placebo after 8 months of treatment (overall risk of sexual transmission: 14/743 [2%] with valaciclovir v 27/741 [4%] with placebo; HR 0.52, 95% CI 0.27 to 0.99; risk of symptomatic HSV-2: 0.5% with valaciclovir v 2.2% with placebo; HR 0.24, 95% CI 0.08 to 0.75). Subgroup analyses found that risks significantly increased if the uninfected partner was female and the duration of the genital HSV-2 infection in the source partner was <2 years (HR for female acquisition: 3.30, 95% CI 1.31 to 8.28; HR for transmission from source partner with shorter duration of genital herpes: 2.89, 95% CI 1.12 to 7.49).

**Harms:**
See individual antiviral drugs, and also see harms of daily maintenance antiviral treatment, p 10.

**Comment:**
Clinical guide: RCTs have shown that daily antiviral treatment decreases the frequency of clinical and subclinical viral shedding (see antiviral treatment at the start of recurrence, p 14).

**OPTION**
**MALE CONDOM USE TO PREVENT SEXUAL TRANSMISSION FROM INFECTED MEN TO UNINFECTED SEXUAL PARTNERS**

**Transmission of infection**

*Compared with no/infrequent condom use* Use of condoms in >25% of sexual acts by men infected with genital herpes may reduce transmission of herpes simplex virus type 2 to their uninfected sexual partners at 18 months (moderate-quality evidence).

**For GRADE evaluation of interventions for genital herpes, see table, p 24.**

**Benefits:**
We found one systematic review (search date not reported),\(^\text{[16]}\) which identified one prospective cohort study.\(^\text{[17]}\) The study (528 people; [98% heterosexual]; 261 men and 267 women in monogamous couples who were serodiscordant for herpes simplex virus type 2 [HSV-2] infection and followed for 18 months, see comment below) found that men infected with genital herpes who used condoms in >25% of sexual acts were at significantly lower risk of infecting their sexual partners with HSV-2 (502 people; adjusted HR 0.09, 95% CI 0.01 to 0.67).\(^\text{[17]}\) Only 61% of couples used condoms during the study, and only 8% (40/502) used them consistently.

**Harms:**
The review\(^\text{[16]}\) and cohort study\(^\text{[17]}\) gave no information on adverse effects.

**Comment:**
In the absence of RCTs, data from other types of studies are necessary to assess the potential effect of condoms on HSV acquisition.
We found one report of results from the screening of women in preparation for an RCT of HCV suppressive therapy (2719 women aged 16 to 35 years in Northern Tanzania and at high risk of acquiring HSV-2) that assessed risk factors for acquisition of HSV-2. The study reported a separate analysis of women aged 16 to 24 years (1143 women) in whom infection was most recent. The study reported that seroprevalence of HSV-2 in this population was 66%. In this subgroup, HSV-2 prevalence was highest among those women who used condoms irregularly (OR 3.5, 95% CI 1.9 to 6.1; includes use "sometimes" compared with always). However, HSV-2 prevalence was lowest among women reporting never having used a condom (OR 0.6, 95% CI 0.4 to 0.9) compared with consistent users, possibly because women never having used a condom also reported fewer partners and were less likely to be exposed to HSV-2.

The systematic review (search date not reported) identified one prospective cohort study that assessed the impact of condom use on development of HSV-2. The study (1843 people who were seronegative for HSV-2; 1345 men and 478 women with multiple partners or one partner with any STI in the previous year) found that the use of condoms in >75% of sexual acts significantly reduced the risk of HSV-2 acquisition over 18 months of follow-up (HR 0.74, 95% CI 0.59 to 0.95).

Clinical guide:
Even with routine counselling, many couples do not regularly use condoms. Trials of different methods of advising people to use condoms or providing condoms could be performed.

**OPTION: FEMALE CONDOMS**

We found no clinically important results from RCTs about the effects of female condoms on prevention of sexual transmission of genital herpes.

**For GRADE evaluation of interventions for genital herpes, see table, p 24.**

**Benefits:** We found no systematic review or RCTs on the effects of female condoms to prevent sexual transmission.

**Harms:** We found no RCTs.

**Comment:** None.

**OPTION: MALE CONDOM USE TO PREVENT SEXUAL TRANSMISSION FROM INFECTED WOMEN TO UNINFECTED MEN**

**Transmission of infection**

**Compared with no/infrequent condom use** We don’t know, based specifically on evidence in serodiscordant couples, whether the use of condoms by uninfected men reduces the risks of acquiring genital herpes from their infected female sexual partners at 18 months (very low-quality evidence).

**Note**
On the basis of observational data and clinical experience of the effects of male condoms to prevent acquisition of genital herpes in uninfected people, there is consensus that they are likely to be beneficial in preventing transmission from infected women to their uninfected partners.

**For GRADE evaluation of interventions for genital herpes, see table, p 24.**

**Benefits:** We found one systematic review (search date not reported), which identified one prospective cohort study. The study (528 people; [98% heterosexual]; 261 men and 267 women in monogamous couples who were serodiscordant for herpes simplex virus type 2 [HSV-2] infection) found no significant difference between male condom use and no male condom use in HSV-2 transmission from infected female partners to uninfected male partners over 18 months' follow-up (502 people; adjusted HR 2.02, 95% CI 0.32 to 12.50).

Only 61% of couples used condoms during the study, and only 8% (40/502) used them consistently.

**Harms:** The review and cohort study gave no information on adverse effects.

**Comment:** We found two systematic reviews (search dates 2008, not reported), which identified studies assessing condom use in uninfected people to prevent any STD and assessed impact on rates of HSV-2 acquisition.
The first review (search date 2008) of prospective studies (including RCTs and cohorts) carried out a meta-analysis of individual patient level data from 6 studies to determine the effect of condoms on preventing acquisition of HSV-2: the review identified three studies of candidate HSV-2 vaccines, one study of antiviral drugs for prevention of transmission of HSV-2, one observational study on STI incidence, and one study of a behavioural intervention to reduce STI acquisition. The review analysed 5384 people who were negative for HSV-2 at baseline, who contributed 2,040,894 follow-up days (median follow-up of 374 days [range 4 to 987]). The review found that a 25% increase in condom use significantly decreased the risk of HSV-2 acquisition (multivariate analysis; HR 0.93, 95% CI 0.85 to 0.99; P = 0.01). Risk of HSV-2 acquisition increased significantly with increasing number of unprotected sex acts per week (univariate analysis stratified by study: HR 1.10, 95% CI 1.02 to 1.19; P = 0.01). However, the review found no significant difference in condom effectiveness between men and women (P = 0.41), despite a higher incidence of HSV-2 acquisition in women (incidence of HSV-2 per 100 person-years: women; 10.8, 95% CI 9.4 to 12.5; men; 5.8, 95% CI 5.1 to 6.6). The analysis of individual patient level data carried out by the review adds to the growing number of condom analyses that use an absolute number of unprotected sexual acts for exposure as opposed to the more traditional measure of percentage of condom use.

The second review (search date not reported) identified one prospective cohort study (1843 people who were seronegative for HSV-2; 1345 men and 478 women with multiple partners or 1 partner with any STI in the previous year), which found that the use of condoms in >75% of sexual acts significantly reduced the risk of HSV-2 acquisition over 18 months’ follow up (HR 0.74, 95% CI 0.59 to 0.95).

Clinical guide:
Even with routine counselling, many couples do not regularly use condoms. Trials of different methods of advising people to use condoms or providing condoms could be performed.

| OPTION | VACCINATION |
|--------|-------------|
| **Transmission of infection** | **Compared with placebo** Recombinant glycoprotein vaccine (gB2 plus gD2) does not reduce the risk of genital infection with herpes simplex virus type 2 (HSV-2) in people at high risk of infection overall, although it may reduce infection in women who are seronegative for HSV-1 and HSV-2 at baseline, and who have regular sexual partners with clinically confirmed genital herpes (moderate-quality evidence). |

**Note**
We found no direct information from RCTs about whether other vaccines are better than no active treatment.

**For GRADE evaluation of interventions for genital herpes, see table, p 24.**

**Benefits:**
Recombinant glycoprotein vaccines versus placebo:
We found no systematic review but we found two RCTs. The first RCT (2393 people seronegative for herpes simplex virus type 2 [HSV-2] and HIV who were at high risk of exposure to genital herpes) compared recombinant glycoprotein vaccine (gB2 plus gD2) versus placebo. It found no significant difference between groups in the proportion of people with HSV infection or positive genital HSV culture (4.2 cases per 100 person-years with glycoprotein vaccine v 4.6 cases per 100 person-years with placebo; P = 0.58). Similarly, it found no significant difference in the duration of initial genital herpes or in the frequency of subsequent recurrences in people who acquired genital HSV-2 infection (duration of initial genital herpes: 7.1 days with glycoprotein vaccine v 6.5 days with placebo; P = 0.45; rate of recurring lesions: 13/24 [54%] with glycoprotein vaccine v 21/33 [64%] with placebo; P = 0.47).

The second RCT (2 studies; 847 HSV-1 and HSV-2 seronegative people in study 1 and 1867 HSV-2 seronegative people in study 2 but at risk from a regular sexual partner with clinically confirmed genital herpes) compared recombinant HSV-2 glycoprotein-D-adjuvant vaccine versus placebo. Both study arms found that recombinant HSV-2 glycoprotein vaccine reduced the risk of infection with HSV compared with placebo in women who were previously uninfected with HSV-1 and HSV-2 (infection defined clinically or by virological or serological investigation; RR for infection 0.27, 95% CI 0.09 to 0.81 in study 1; 0.26, 95% CI 0.07 to 0.91 in study 2). However, no significant effect was found in women who were infected with HSV-1 at baseline or in men (in women with HSV-1: RR for infection 2.06, 95% CI 0.51 to 8.03; in men: RR 1.11, 95% CI 0.47 to 2.61 in study 1; RR 1.10, 95% CI 0.53 to 2.27 in study 2).

**Other types of vaccine:**
We found no systematic review or RCTs on other types of vaccine.
**Harms:** Recombinant glycoprotein vaccines versus placebo:
The first RCT reported the vaccine to be safe and well tolerated, with frequencies of local and systemic reactions similar to those stated in the literature. In the second RCT, the frequency of soreness at the injection site severe enough to prevent people from engaging in normal actions was higher with vaccine (5%) than with placebo (3% in study 1 and 1% in study 2; significance not reported). The study found no major differences between the two groups in the frequency and type of reported symptoms or withdrawal rates (no statistical values reported).

**Other types of vaccine:**
We found no RCTs.

**Comment:** Glycoprotein vaccines differ not only in the choice of recombinant HSV molecules but also in the use of adjuvants. The use of different adjuvants may explain the inconsistent efficacy results of otherwise similar glycoprotein vaccines.

**QUESTION** What are the effects of interventions to prevent transmission of herpes simplex virus from mother to neonate?

**OPTION** CAESAREAN DELIVERY TO PREVENT NEONATAL HERPES

We found no clinically important results from RCTs about the effects of caesarean delivery on mother-to-baby transmission of genital herpes in mothers with genital lesions at term.

**Adverse effects**
Caesarean delivery carries the risk of increased maternal morbidity and mortality.

For GRADE evaluation of interventions for genital herpes, see table, p 24.

**Benefits:** We found no systematic review or RCTs that assessed the effects of caesarean delivery on the risk of mother-to-child transmission of herpes simplex virus (HSV).

**Harms:** Caesarean delivery can be associated with maternal morbidity (8.5% of women having caesarean section). Caesarean delivery can be associated with maternal morbidity (8.5% of women having caesarean section).

**Comment:** Clinical guide:
The available evidence suggests that efforts to prevent neonatal HSV infection should focus on preventing infection in late pregnancy. The absolute risk of neonatal infection is high (AR 41%, 95% CI 26% to 56%) in babies born to women who acquire infection near the time of labour and low (AR <3%) in women with established infection, even in those who have recurrence at term. Most women who acquire infection towards the end of pregnancy are undiagnosed, and most cases of neonatal HSV infection are acquired from women without a history of genital herpes. Case studies indicate that the transmission of HSV-2 can occur, despite caesarean delivery. An observational study carried out in the US (prospective cohort; 202 women from whom HSV was isolated at the time of labour) found that isolation of HSV from women at the time of labour was a major risk factor for neonatal infection with HSV (OR 346, 95% CI 125 to 956); 5% (10/202) of women had neonates with HSV infection. Caesarean delivery was found to significantly reduce mother-to-infant HSV transmission rate compared with vaginal delivery (1/85 [1%] with caesarean delivery v 9/117 [8%] with vaginal delivery; OR 0.14, 95% CI 0.02 to 1.08; P = 0.047). Countries vary in their approach to obstetric management of women with active recurrent genital herpes at term. In the US and the UK, these women are advised to have a caesarean delivery, with its attendant risks to the mother. In the Netherlands, women presenting with recurrent genital lesions at delivery have been allowed vaginal birth since 1987. This policy has not resulted in an increase in neonatal herpes (26 cases from 1981–1986 and 19 cases from 1987–1991).

**OPTION** ANTIVIRAL MAINTENANCE TREATMENT IN LATE PREGNANCY (AT LEAST 36 WEEKS’ GESTATION) TO PREVENT TRANSMISSION OF INFECTION TO NEONATES FROM WOMEN WITH A HISTORY OF GENITAL HERPES

**Transmission of infection**
Compared with placebo We cannot infer whether oral antiviral agents given in late pregnancy are effective at reducing transmission of infection because of the rarity of neonatal transmission of herpes simplex virus (HSV) from women with recurrent genital herpes (moderate-quality evidence).

**Recurrence of infection**
Compared with placebo Oral antiviral agents (aciclovir and valaciclovir) are more effective at reducing the recurrence of infection at term in women with first or recurrent episodes of genital HSV during pregnancy (high-quality evidence).
Rate of caesarean section

**Compared with placebo** Oral antiviral agents (aciclovir and valaciclovir) are more effective at reducing rates of caesarean section carried out because of genital herpes (high-quality evidence).

**For GRADE evaluation of interventions for genital herpes, see table, p 24.**

**Benefits:**

We found one systematic review (search date 2007, 7 RCTs, 1249 pregnant women with a history of genital herpes at 36 weeks’ gestation) assessing the effects of oral antiviral maintenance treatment in late pregnancy. [26]

**Rates of neonatal herpes:**

The review reported that there were no cases of symptomatic neonatal herpes simplex virus (HSV) in either the treatment or control group in any of the identified RCTs (7 RCTs; 0/646 [0%] with antivirals v 0/594 [0%] with placebo or no treatment), and, therefore, it was not possible to calculate the effect of antepartum antiviral prophylaxis on the prevention of transmission of HSV. [26] Given the rarity of neonatal transmission of HSV from women with recurrent genital herpes, the meta-analysis is underpowered to identify a statistically significant reduction in neonatal infection.

**Rate of recurrent genital herpes at term:**

The review found that, compared with placebo, antiviral prophylaxis (aciclovir or valaciclovir) significantly reduced the proportion of women with recurrence of genital herpes at delivery (7 RCTs, 1249 women; 25/651 [4%] with antivirals v 87/598 [15%] with placebo; RR 0.28, 95% CI 0.18 to 0.43). [26] Subgroup analyses by antiviral given found that both aciclovir (800 mg or 1200 mg daily) and valaciclovir (500 mg twice daily) significantly reduced the rate of genital herpes recurrence at delivery compared with placebo (aciclovir: 5 RCTs, 799 women; 15/424 [4%] with aciclovir v 58/375 [15%] with placebo; RR 0.25, 95% CI 0.15 to 0.43; valaciclovir: 2 RCTs, 450 women; 10/227 [4%] with valaciclovir v 29/223 [13%] with placebo; RR 0.34, 95% CI 0.17 to 0.68).

**Rate of caesarean delivery for genital herpes:**

The review found that the proportion of women undergoing caesarean delivery for genital herpes was significantly smaller with antiviral prophylaxis compared with placebo (7 RCTs, 1249 women; 25/651 [4%] with antivirals v 83/598 [14%] with placebo; RR 0.30, 95% CI 0.20 to 0.45). [26] Subgroup analyses by antiviral given found that both aciclovir (800 mg or 1200 mg daily) and valaciclovir (500 mg twice daily) significantly reduced the rate of caesarean delivery for genital herpes compared with placebo (aciclovir: 15/424 [4%] with aciclovir v 55/375 [15%] with placebo; RR 0.27, 95% CI 0.16 to 0.46; valaciclovir: 10/227 [4%] with valaciclovir v 28/223 [13%] with placebo; RR 0.35, 95% CI 0.17 to 0.70). The review noted moderate heterogeneity in the subgroup analysis of aciclovir (I² = 54%; P = 0.07; statistical significance of heterogeneity not defined). The review reported that a potential source of heterogeneity could be the differences in aciclovir dosing regimens.

Caesarean delivery was considered “indicated” in the presence of prodromal symptoms or with genital lesions consistent with genital herpes. [24] However, in the RCTs identified by the review, the decision to perform a caesarean delivery was left to the discretion of the clinician in attendance at delivery. In one of the RCTs included in the meta-analysis, delivery by elective caesarean section was performed if a woman experienced a herpes recurrence later than 38 weeks’ gestation. [27] In another RCT identified by the review, one woman had a caesarean delivery for genital herpes without a clinical recurrence at term, and two women with genital lesions delivered vaginally. [28] In a third RCT identified by the review, three women in the placebo group and one woman in the aciclovir group did not have a caesarean delivery because their lesions were distant from the birth canal. [29]

**Harms:**

The review did not pool data on adverse effects, but highlighted individual RCTs that reported on neonatal and maternal adverse effects. [26]

Two RCTs identified by the review reported neonatal adverse effects associated with exposure to prophylactic antiviral treatment. [30] [31] The identified RCTs were underpowered to detect rare adverse effects in newborn infants, such as an increase in aciclovir-related obstructive uropathy or infection. Neonatal adverse effects reported in the RCTs included oligohydramnios, [30] impaired renal function, [30] [31] serum chemistries, [30] [31] and neutropenia. [30] [41] One RCT identified by the review (126 infants whose mothers had been treated) reported that mean level of aspartate aminotransferase was significantly higher with placebo than with antiviral prophylactic treatment with valaciclovir (mean: 76 U/L with valaciclovir v 94 U/L with placebo; P = 0.01). [30] However, the second RCT reported that there was no significant difference in the proportion of infants with transaminase levels >2 standard deviations above the mean (3/66 [5%] with valaciclovir v 5/60 [8%] with placebo; P = 0.38). [31] The RCTs reported that no infants in either treatment or placebo groups had white blood cell counts <4000/mm³; data from complete blood counts were available for 238 infants (123 receiving valaciclovir and 115 receiving placebo). [30] [31]
Two RCTs identified by the review reported on maternal adverse effects associated with antiviral prophylaxis. The identified RCTs were underpowered to detect rare adverse effects in mothers. One RCT identified by the review reported no evidence of haematological or biochemical toxicity. One RCT reported that antiviral treatment was associated with increased nausea, vomiting, diarrhoea, headache, bitter taste, and skin rash. The RCT reported that symptoms occurred in two people in the treatment group and 13 people in the placebo group. No studies assessed maternal acceptability of the intervention or maternal anxiety.

Comment: None.

**OPTION**

**SEROLOGICAL SCREENING AND COUNSELLING TO PREVENT ACQUISITION OF HERPES SIMPLEX VIRUS IN LATE PREGNANCY (AT LEAST 36 WEEKS’ GESTATION)**

We found no clinically important results from RCTs about the effects of either serological screening or counselling to prevent maternal infection with genital herpes in late pregnancy.

For GRADE evaluation of interventions for genital herpes, see table, p 24.

**Benefits:**
We found no systematic review or RCTs that assessed either serological screening with type-specific assays to identify women at risk for acquisition of herpes simplex virus (HSV) infection in late pregnancy, or counselling to avoid genital–genital and oral–genital contact in late pregnancy.

**Harms:**
We found no RCTs.

**Comment:** None.

**QUESTION**

**What are the effects of antiviral treatment in people with a first episode of genital herpes?**

**OPTION**

**ANTIVIRAL TREATMENT (ORAL) VERSUS PLACEBO**

**Severity of attack**
*Compared with placebo* Oral aciclovir treatment is more effective at decreasing the duration of lesions, and symptoms in people with a first episode of genital herpes (moderate-quality evidence).

**Viral shedding**
*Compared with placebo* Oral aciclovir treatment is more effective at decreasing the duration of viral shedding in people with a first episode of genital herpes (moderate-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.

**Benefits:**
Oral aciclovir versus placebo:

We found no systematic review but we found three RCTs.

The largest RCT (180 people, 119 of whom had a first episode of genital herpes) compared aciclovir (200 mg 5 times daily for 10 days) versus placebo. Analysis in people with a first episode of genital herpes (119 people) found that aciclovir significantly decreased the time to complete healing of lesions (12 days with aciclovir v 14 days with placebo; P = 0.005), reduced the formation of new lesions (percentage of people with new lesions after 48 hours of therapy: 18% with aciclovir v 62% with placebo; P = 0.001), and reduced the duration of pain (median: 5 days with aciclovir v 7 days with placebo; P = 0.05) and viral shedding (median: 2 days with aciclovir v 9 days with placebo; P <0.001) compared with placebo. The RCT excluded 30/180 (17%) people before analysis: 10 people for not completing the study protocol, 12 because of suspected past infection, and 8 because herpes simplex virus was not isolated.

The second RCT (31 people with first-episode genital herpes) compared aciclovir (200 mg 5 times daily for 5 days) versus placebo. It found that, compared with placebo, aciclovir significantly reduced the duration of viral shedding and pain (median duration of viral shedding: 1 day with aciclovir v 3 days with placebo; P <0.01; median duration of pain: 4 days with aciclovir v 8 days with placebo; P <0.05). Aiclovir also reduced the median time to healing, but this did not reach significance (6 days with aciclovir v 11 days with placebo; P = 0.06).

The third RCT (48 people [31 women, 17 men]) compared aciclovir (200 mg 5 times daily for 10 days) versus placebo. It found that, compared with placebo, aciclovir significantly reduced the duration of viral shedding and to crusting (mean duration of viral shedding in women: 4.9 days...
with aciclovir v 17.7 days with placebo; P = 0.001; mean duration of viral shedding in men: 6 days with aciclovir v 15 days with placebo; P = 0.02; mean time to crusting in women: 8.8 days with aciclovir v 15.0 days with placebo; P = 0.01; mean time to crusting in men: 5 days with aciclovir v 15 days with placebo; P = 0.01). No precise estimates of effectiveness were available because of the small numbers included.

Harms: Adverse effects were rare and similar in the placebo and treatment groups. \[32\] \[33\] \[34\]

Comment: None.

**OPTION** DIFFERENT TYPES OF ORAL ANTIVIRAL TREATMENT

**Severity of attack**

**Valaciclovir compared with aciclovir** Oral valaciclovir and oral aciclovir are equally effective at reducing symptoms in people with first episodes of genital herpes (high-quality evidence).

**Viral shedding**

**Valaciclovir compared with aciclovir** Oral valaciclovir and oral aciclovir are equally effective at reducing duration of viral shedding in people with first episodes of genital herpes (high-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.

**Benefits:**

Valaciclovir versus aciclovir:

We found no systematic review, but we found one RCT (643 people) comparing oral valaciclovir (1000 mg twice daily for 10 days) versus oral aciclovir (200 mg 5 times daily for 10 days). \[35\] The RCT found no significant difference between treatments in duration of viral shedding, time to healing, and time to resolution of all symptoms (duration of viral shedding: 3 days with valaciclovir v 3 days with aciclovir; HR 1.00, 95% CI 0.84 to 1.18; P = 0.99; time to healing: 9 days with valaciclovir v 9 days with aciclovir; HR 1.08, 95% CI 0.92 to 1.27; P = 0.35; time to resolution of all symptoms: 9 days with valaciclovir v 9 days with aciclovir; HR 1.02, 95% CI 0.85 to 1.22; P = 0.85).

Harms: Headache was reported in 74/643 (12%) and nausea in 38/643 (6%) people receiving treatment and there was no significant difference between the aciclovir and valaciclovir groups (headache: 41/74 [55%] with valaciclovir v 33/74 [45%] with aciclovir; nausea: 18/38 [47%] with valaciclovir v 20/38 [53%] with aciclovir; significance assessment not reported for either adverse effect; reported as not significant). \[35\]

Comment: None.

**QUESTION** What are the effects of interventions to reduce the impact of recurrence?

**OPTION** DAILY ORAL ANTIVIRAL TREATMENT TO REDUCE RECURRENCE

**Recurrence of infection**

**Antivirals compared with placebo** Daily maintenance treatment with oral antivirals (aciclovir, valaciclovir, and famciclovir) is more effective at reducing the proportion of people with recurrence of genital herpes in people with a history of recurrence (moderate-quality evidence).

**Aciclovir compared with placebo** Daily maintenance treatment with oral aciclovir is more effective at reducing the frequency of recurrences of genital herpes at up to 18 months (high-quality evidence).

**Famciclovir compared with placebo** Daily maintenance treatment with oral famciclovir seems more effective at reducing the frequency of recurrences of genital herpes at 4 to 12 months (moderate-quality evidence).

**Valaciclovir compared with placebo** Daily maintenance treatment with oral valaciclovir is more effective at reducing the frequency of recurrences of genital herpes, and at increasing the time to recurrence in people with a history of frequent recurrence of genital herpes and in people with recently acquired genital herpes (high-quality evidence).

**Famciclovir compared with valaciclovir** Famciclovir and valaciclovir seem equally effective at reducing the frequency of recurrence of genital herpes at 4 months and at increasing time to first recurrence in people with a history of clinical recurrence (moderate-quality evidence).

**Viral shedding**
Aciclovir compared with placebo Daily treatment with oral aciclovir may be more effective at reducing viral shedding in women with genital herpes simplex virus type 2 infection of <2 years' duration and a history of at least one recurrence (low-quality evidence).

Famciclovir compared with placebo Daily treatment with oral famciclovir may be more effective at reducing viral shedding in people with a history of symptomatic genital herpes (very low-quality evidence).

Valaciclovir compared with placebo Daily treatment with oral valaciclovir may be more effective at reducing percentage of days with viral shedding in people with a history of recurrence of genital herpes (low-quality evidence).

Famciclovir compared with valaciclovir Famciclovir and valaciclovir may be equally effective at reducing the number of people with viral shedding during 4 months in people with a history of clinical recurrence, but, in those with shedding, famciclovir may be less effective at reducing the number of days of viral shedding (low-quality evidence).

Quality of life
Aciclovir compared with placebo Daily treatment with oral aciclovir is more effective at improving quality of life at 3 months in people with genital herpes (high-quality evidence).

Valaciclovir compared with placebo Daily treatment with oral valaciclovir (various doses) is more effective at improving quality of life at 3 months in people with genital herpes (high-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.

Benefits: Any antiviral versus placebo:
We found one systematic review (search date 2004, 14 RCTs, 6158 people with recurrent genital herpes), [36] which compared aciclovir (10 RCTs, 2382 people), valaciclovir (3 RCTs, 3078 people), and famciclovir (2 RCTs, 832 people) versus placebo; some RCTs had multiple arms. The review found that a significantly smaller proportion of people developed at least one recurrence of genital herpes during follow-up with oral antivirals compared with placebo (14 RCTs, 6158 people; 1790/4037 [44%] with antivirals v 1950/2255 [86%] with placebo; RR 0.53, 95% CI 0.51 to 0.55). The review limited inclusion to RCTs in English language. The review found that there was significant statistical heterogeneity among RCTs (P <0.001); it reported that potential sources of heterogeneity included variation in the drug regimens analysed (including differences in doses and number of daily drug intakes). The review carried out subgroup analyses of the included antivirals, which, because of the heterogeneity present in the overall analysis, we report below. We also identified additional and subsequent RCTs for the individual antivirals, which we also report below.

Aciclovir versus placebo:
We found one systematic review (search date 2004), [36] three additional RCTs, [37] [38] [39] and one subsequent RCT. [11]

The review found that aciclovir (10 RCTs, 2382 people) significantly reduced the rate of genital herpes recurrence compared with placebo (proportion of people with at least 1 recurrence during follow-up: 490/1274 [38%] with aciclovir v 1033/1108 [93%] with placebo; RR 0.47, 95% CI 0.43 to 0.49). [36] The review found that there was significant statistical heterogeneity among RCTs in the analysis (P <0.001); the review reported that potential sources of heterogeneity included differences in doses and number of daily drug intakes. The meta-analysis carried out by the review included aciclovir at doses of 200 mg twice a day, 200 mg three times a day, 200 mg 4 times a day, 200 mg 5 times a day, 400 mg twice a day, and 800 mg daily. Follow-up in the RCTs identified by the review ranged from 3 months to 12 months. [36]

The first additional RCT (1146 people) also found that aciclovir 400 mg twice daily significantly reduced recurrence at 1 year compared with placebo (recurrence rate: 2% with aciclovir v 13% with placebo; P <0.0001). [37] Of 210 adults in the RCT who completed 5 years of continuous treatment with aciclovir, 53% to 70% were free from recurrence each year.

The second additional RCT (34 women with genital herpes simplex virus type 2 [HSV-2] infection of <2 years’ duration; all women had had at least 1 recurrence of genital herpes) found that aciclovir (400 mg twice daily for 70 days) significantly reduced viral shedding compared with placebo (proportion of women with at least 1 episode of subclinical viral shedding: 3/17 [18%] with aciclovir v 15/17 [88%] with placebo; P <0.001). [38] It also found that, compared with placebo, aciclovir reduced viral shedding by 95% on days with reported lesions and by 94% on days without lesions.

The third additional RCT (1479 people) [39] evaluated the effects of valaciclovir and aciclovir on quality of life, as assessed by a genital herpes quality-of-life scale (range of score from 0 [worst possible score] to 60 [best possible score]): [40] 1349 people completed the baseline questionnaire. The RCT was a 5-armed RCT comparing valaciclovir 250 mg twice daily (249 people) versus
valaciclovir 1000 mg once daily (245 people) versus valaciclovir 500 mg once daily (240 people) versus valaciclovir 250 mg once daily (247 people) versus aciclovir twice daily (243 people) versus placebo (123 people). The RCT found that twice daily aciclovir treatment significantly improved health-related quality of life scores after 3 months compared with placebo (mean difference in quality of life score from placebo 5.1, 95% CI 2.9 to 7.4). [39]

The subsequent RCT (3277 HIV-negative, HSV-2-seropositive people) found that aciclovir (400 mg twice daily) significantly reduced genital ulcer recurrence at 18 months compared with placebo (3172 people in this analysis: data reported as events/person-years: 574/1936 person-years with aciclovir v 1090/1971 person-years with placebo; RR 0.53, 95% CI 0.46 to 0.62). [11] Of the 3172 people analysed, 801 people self-reported genital ulcer disease in the 3 months before enrolment (381/1581 [24%] in the aciclovir group v 420/1591 [26%] in the placebo group; P >0.05).

**Famciclovir versus placebo:**
We found one systematic review (search date 2004) [36] and one subsequent RCT. [41]

The review found that famciclovir (2 RCTs, 832 people) significantly reduced the rate of genital herpes recurrence compared with placebo (proportion of people with at least 1 recurrence during follow-up: 276/654 [42%] with famciclovir v 132/178 [74%] with placebo; RR 0.58, 95% CI 0.50 to 0.65). [36] The review found that there was significant statistical heterogeneity in the analysis (P <0.001): the review reported that potential sources of heterogeneity included differences in doses and number of daily drug intakes. The meta-analysis carried out by the review included various doses of famciclovir: 125 mg twice a day, 250 mg once a day, 125 mg three times a day, 250 mg twice a day, 500 mg once a day, and 250 mg three times a day. The review reported that a trend towards a dose effect was observed: the review reported that the 125 mg once daily dosing was not effective, and there was a clear dose-effect response between total doses of 250 mg daily and 750 mg daily. Follow-up in the RCTs identified by the review was 4 months in one RCT and 12 months in the other. [36]

The subsequent RCT (129 people seropositive for HSV-2, with or without a history of symptomatic genital herpes) compared famciclovir (250 mg twice daily) for 42 days versus placebo in a crossover design; after 42 days of treatment with famciclovir or placebo, there followed a 14-day washout period before crossover to 42 days of treatment with the other regimen. [41] The RCT carried out a subgroup analysis in people with a clinical history of genital herpes (61 people). The RCT found that a smaller proportion of people had a genital lesion during treatment with famciclovir compared with placebo (post-crossover results; 10/58 [17%] with famciclovir v 23/59 [39%] with placebo; significance not assessed). The RCT reported that, compared with placebo, famciclovir resulted in a 71% reduction in total days with genital lesions (total days with genital lesions/total number of days: 60/2251 [3%] with famciclovir v 212/2334 [9%] with placebo; significance not assessed). The RCT found that HSV viral shedding was detected (at least once) in a smaller proportion of people during treatment with famciclovir compared with placebo (post-crossover results: 27/56 [48%] with famciclovir v 40/58 [69%] with placebo; significance not assessed).

**Valaciclovir versus placebo:**
We found one systematic review (search date 2004), [36] one additional RCT, [39] and two subsequent RCTs. [42] [43]

The review found that valaciclovir (3 RCTs, 3078 people) significantly reduced the rate of genital herpes recurrence compared with placebo (proportion of people with at least 1 recurrence during follow-up: 1024/2109 [49%] with valaciclovir v 785/969 [81%] with placebo; RR 0.57, 95% CI 0.53 to 0.59). [36] The review found that there was significant statistical heterogeneity among the RCTs in the analysis (P <0.001); the review reported that potential sources of heterogeneity included differences in doses and number of daily drug intakes. The meta-analysis carried out by the review included various doses of valaciclovir: 1000 mg once daily, 500 mg once daily, 250 mg once daily, and 250 mg twice daily. The review reported that all doses showed efficacy, with a dose-dependent response suggesting 250 mg daily was less effective than 500 mg daily. Follow-up in the RCTs identified by the review was 4 months to 12 months. [36]

The additional RCT (1479 people) [39] evaluated the effects of valaciclovir and aciclovir on quality of life, as assessed by a genital herpes quality of life scale (range of score from 0 [worst possible score] to 60 [best possible score]): [40] 1349 people completed the baseline questionnaire. The RCT was a 5-armed RCT comparing valaciclovir 250 mg twice daily (249 people) versus valaciclovir 1000 mg once daily (245 people) versus valaciclovir 500 mg once daily (240 people) versus valaciclovir 250 mg once daily (247 people) versus aciclovir (243 people) versus placebo (123 people). The RCT found that all doses of valaciclovir significantly improved health-related quality of life scores after 3 months compared with placebo (mean difference in quality of life score from placebo: valaciclovir 250 mg twice daily: 4.8, 95% CI 1.7 to 6.3; valaciclovir 1000 mg once daily: 12.0, 95% CI 8.8 to 14.6; valaciclovir 500 mg once daily: 8.2, 95% CI 5.0 to 11.4; valaciclovir 250 mg once daily: 5.3, 95% CI 2.5 to 8.0; aciclovir: 3.0, 95% CI 0.3 to 5.7; placebo: -0.6, 95% CI -3.5 to 2.4).

[36] The review identified 10 RCTs for analysis, including the additional RCT (1479 people), an additional RCT (1479 people), and one subsequent RCT. [39] The review found that there was significant statistical heterogeneity among the RCTs in the analysis (P <0.001); the review reported that potential sources of heterogeneity included differences in doses and number of daily drug intakes. The meta-analysis carried out by the review included various doses of valaciclovir: 1000 mg once daily, 500 mg once daily, 250 mg once daily, and 250 mg twice daily. The review reported that all doses showed efficacy, with a dose-dependent response suggesting 250 mg daily was less effective than 500 mg daily. Follow-up in the RCTs identified by the review was 4 months to 12 months. [36]
Harms:
The systematic review and two RCTs gave no information on adverse effects.

One RCT reported that aciclovir, famciclovir, and valaciclovir were well tolerated. People taking aciclovir were followed for up to 7 years, and those taking famciclovir and valaciclovir for up to 1 year. Nausea and diarrhoea were infrequent, and people rarely discontinued treatment because of adverse effects.

One RCT assessing the effects of famciclovir found that similar proportions of people in the famciclovir and placebo groups experienced adverse effects. The most commonly reported adverse effects were headache, nausea, sinusitis, diarrhoea, and fatigue (headache: 6.6% with famciclovir v 4.2% with placebo; nausea: 5.8% with famciclovir v 2.5% with placebo; sinusitis: 5.0% with famciclovir v 3.4% with placebo; diarrhoea: 4.1% with famciclovir v 2.5% with placebo; fatigue: 4.1% with famciclovir v 0.8% with placebo; absolute numbers not reported for any outcome; significance of between-group difference not assessed for any outcome).

One RCT assessing valaciclovir found that similar proportions of people in the valaciclovir and placebo groups experienced adverse effects. The most commonly reported adverse effect in both groups was headache (18% with valaciclovir v 24% with placebo; absolute numbers not reported; significance not assessed).
The first RCT comparing famciclovir versus valaciclovir found that headache was the most common adverse effect reported, occurring in a similar proportion of people in the famciclovir and valaciclovir groups (12.6% with famciclovir vs 12.4% with valaciclovir; significance not assessed; absolute numbers not reported). Headache was also the most common adverse effect reported in the second RCT comparing famciclovir versus valaciclovir, occurring in a similar proportion of people in each group (15% with famciclovir vs 14% with valaciclovir; significance not assessed; absolute numbers not reported).

We found no trials evaluating whether daily maintenance treatment increases high-risk sexual behaviour.

We found no evidence that daily treatment with aciclovir results in emergence of aciclovir-resistant HSV during or after stopping treatment in healthy adults.

Comment: In the past, there was some controversy regarding the biological and clinical meaning of asymptomatic HSV-2 infection. However, a study by Wald et al in 2000 suggested that the pattern, sites, and frequency of subclinical reactivation of infection in people seropositive for HSV-2 was similar to that in people with symptomatic infection. Therefore, people seropositive for HSV-2 are treated in the same way as those with recurrent symptomatic infection and we include both groups in this option.

OPTION

**ORAL ANTIVIRAL TREATMENT TAKEN AT THE START OF RECURRENTNESS**

Severity of attack

*Aciclovir compared with placebo* Oral aciclovir taken at the start of recurrence is more effective at reducing the duration of lesions in people with recurrent genital herpes (moderate-quality evidence).

*Famciclovir compared with placebo* Oral famciclovir taken at the start of recurrence is more effective at reducing the duration of lesions in people with recurrent genital herpes (moderate-quality evidence).

*Valaciclovir compared with placebo* Oral valaciclovir taken at the start of recurrence is more effective at reducing the duration of lesions in people with recurrent genital herpes (high-quality evidence).

*Famciclovir compared with aciclovir* Oral famciclovir and aciclovir when taken at the start of recurrence are equally effective at reducing time to lesion healing in people with recurrent genital herpes (high-quality evidence).

*Famciclovir compared with valaciclovir* Self-initiated treatment with oral famciclovir at the start of prodromal symptoms seems as effective as self-initiated treatment with oral valaciclovir at reducing time to healing of all non-aborted lesions and increasing the proportion of aborted lesions in people with recurrent genital herpes (moderate-quality evidence).

*Valaciclovir compared with aciclovir* Oral valaciclovir and oral aciclovir taken at the start of recurrence are equally effective at reducing healing time and duration of symptoms in people with recurrent genital herpes (high-quality evidence).

*Famciclovir for 2 days compared with 5 days* Oral famciclovir for 2 days self-initiated (within 12 hours of signs or symptoms) seems as effective as self-initiated famciclovir for 5 days at reducing the proportion of recurrences with lesions present at 5.5 days and improving symptom severity over 5 days in people with recurrent genital herpes (moderate-quality evidence).

*Valaciclovir for 3 days compared with 5 days* Oral valaciclovir for 3 days is as effective at reducing the duration of symptoms compared with oral valaciclovir for 5 days (moderate-quality evidence).

Viral shedding

*Aciclovir compared with placebo* Oral aciclovir taken at the start of recurrence is more effective at reducing the duration of viral shedding in people with recurrent genital herpes (moderate-quality evidence).

*Famciclovir compared with placebo* Oral famciclovir taken at the start of recurrence is more effective at reducing the duration of viral shedding in people with recurrent genital herpes (moderate-quality evidence).

*Valaciclovir compared with placebo* Oral valaciclovir taken at the start of recurrence is more effective at reducing the duration of viral shedding in people with recurrent genital herpes (high-quality evidence).

*Valaciclovir compared with aciclovir* Oral valaciclovir and oral aciclovir taken at the start of recurrence are equally effective at reducing the duration of viral shedding in people with recurrent genital herpes (high-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.
Benefits: Antivirals versus placebo:

Aciclovir versus placebo:
We found no systematic review but we found one non-systematic review (number of RCTs not reported, 650 people) [47] and one subsequent RCT. [48] The RCTs in the review compared oral aciclovir started at the first sign of recurrence (200 mg 5 times daily or 800 mg twice daily, for 5 days) versus placebo. [47] The review found that aciclovir reduced the period of viral shedding and duration of lesions compared with placebo (period of viral shedding: 1 day with aciclovir v 2 days with placebo; duration of lesions: 5 days with aciclovir v 6 days with placebo; significance not assessed). [48] The subsequent RCT (131 people with at least 3 recurrences in the previous 12 months, observed for 1 or more recurrence) found that aciclovir (800 mg 3 times daily for 2 days) significantly reduced the duration of episodes, and viral shedding compared with placebo (median duration of lesions: 4 days with aciclovir v 6 days with placebo; P = 0.001; median duration of episodes: 4 days with aciclovir v 6 days with placebo; P < 0.001; median duration of viral shedding: 25.0 hours with aciclovir v 58.5 hours with placebo; P = 0.04). [50]

Famciclovir versus placebo:
We found one systematic review (search date not reported; 1 RCT, 467 people). [49] and two subsequent RCTs. [50] [51] The RCT identified by the review found that oral famciclovir (125–500 mg twice daily for 5 days) significantly reduced the duration of lesions (median: 4 days with famciclovir v 5 days with placebo; P value not reported) and viral shedding (2 days with famciclovir v 3 days with placebo; P value not reported) compared with placebo. [49] One subsequent RCT (308 people presenting within 6.5 hours of recurrence of symptoms) of clinic-initiated treatment compared oral famciclovir (125, 250, or 500 mg twice daily for 5 days) versus placebo. [50] The RCT found that, compared with placebo, all doses of famciclovir significantly reduced the time to cessation of viral shedding (125 mg; HR 3.29, 95% CI 2.19 to 4.95; 250 mg: HR 3.26, 95% CI 2.16 to 4.92; 500 mg: HR 3.56, 95% CI 2.29 to 5.53) and to complete healing (125 mg: HR 1.48, 95% CI 1.06 to 2.08; 250 mg: HR 1.74, 95% CI 1.23 to 2.46; 500 mg: HR 1.79, 95% CI 1.26 to 2.53). [50] One subsequent RCT (329 people with recurrent herpes simplex virus type 2 [HSV-2] and at least 4 recurrences in the previous 12 months) compared famciclovir (1000 mg twice daily for 1 day) versus placebo. [51] The RCT found that self-initiated oral famciclovir significantly decreased the time to healing of aborted and non-aborted genital lesions compared with placebo (3.5 days with famciclovir v 5.0 days with placebo; P <0.001).

Valaciclovir versus placebo:
We found one systematic review (search date not reported; 1 RCT, 987 people). [49] The RCT identified by the review compared oral valaciclovir (500 mg or 1000 mg twice daily for 5 days) versus placebo. The RCT found that self-initiated oral valaciclovir significantly decreased episode duration and viral shedding compared with placebo (median episode duration: 4 days with valaciclovir v 6 days with placebo; HR 1.9, 95% CI 1.6 to 2.3; median viral shedding: 2 days with valaciclovir v 4 days with placebo; HR 2.9, 95% CI 2.1 to 3.9). Self-initiated oral valaciclovir increased the rate of aborted recurrences compared with placebo (31% with valaciclovir v 21% with placebo; RR 1.5, 95% CI 1.1 to 1.9).

Antivirals versus each other:
Famciclovir versus aciclovir:
We found one RCT (204 people), which found no significant difference in time to lesion healing between oral famciclovir and aciclovir (mean: 5.1 days with famciclovir v 5.4 days with aciclovir; mean difference +0.3 days, 95% CI –0.3 days to +0.8 days). [52]

Famciclovir versus valaciclovir:
We found one RCT (1179 people with HSV and experiencing at least 4 recurrences of genital herpes in the preceding 12 months) that compared self-initiated treatment (treatment initiated within 6 hours of onset of symptoms) with oral famciclovir (1000 mg twice daily) for a single day versus oral valaciclovir (500 mg twice daily) for 3 days. [53] Of 1179 people randomised, 751 people initiated treatment. The RCT found no significant difference between the famciclovir and valaciclovir regimens in time to healing of all non-aborted (progression of lesions beyond the papule stage) genital herpes lesions (502 people in this analysis; median time to healing: 4.25 days with famciclovir v 4.08 days with valaciclovir; median treatment difference +0.16 days, 95% CI –0.15 days to +0.60 days). The RCT reported that a similar proportion of people in each group experienced aborted lesions (121/370 [33%] with famciclovir v 128/381 [34%] with valaciclovir; significance not assessed). A further report of the RCT found no significant difference between the antiviral regimens in the median time to next recurrence from treatment initiation (analysis of 457 people with a second recurrence: 33.5 days with famciclovir v 38.0 days with valaciclovir; median of differences –3.00 days, 95% CI –8.00 days to +2.00 days). [54]
Valaciclovir versus aciclovir:
We found one systematic review (search date not reported, 1 RCT, 739 people). The included RCT compared oral valaciclovir (500 mg twice daily for 5 days) versus aciclovir (200 mg 5 times daily for 5 days). It found no significant difference in healing time, symptom time, or viral shedding between the two antiviral drugs (healing time: HR 0.96, 95% CI 0.80 to 1.14; symptom duration: HR 0.93, 95% CI 0.79 to 1.08; viral shedding: HR 0.98, 95% CI 0.75 to 1.27).

Different durations of the same antiviral versus each other:
Famciclovir for 2 days versus 5 days:
We found one RCT. The RCT (873 people with either >2 recurrences of genital herpes in the past 12 months, 1 recurrence in the past 6 months, or their first episode within the previous 6 months) compared self-initiated treatment (within 12 hours of any signs or symptoms) versus immediate treatment with famciclovir 500 mg followed by 250 mg twice daily for 2 days (2-day course) or versus famciclovir 125 mg twice daily for 5 days (5-day course). If people self-initiated treatment and presented for follow-up 5.5 days after initiation of treatment, they were re-randomised and supplied with antiviral treatment for a potential second recurrence; results are therefore presented in terms of recurrence. The RCT found no significant difference between treatment with famciclovir for 2 days and for 5 days in the proportion of recurrences with lesions present 5.5 days after initiating treatment (1024 recurrences in this analysis [516 recurrences in the 2-day group and 508 recurrences in the 5-day group]: 24% with 2 days of famciclovir v 28% with 5 days of famciclovir; upper 97.5% CI 2%; absolute numbers not reported). The upper CI limit is within the predefined limit of 10% difference for non-inferiority: the RCT was designed to assess whether "the 2-day famciclovir course would have a less-than or equal to10 percentage point difference in the proportion of recurrences healed at 5.5 days when compared with the 5-day course". The RCT found no significant difference between antiviral regimens in patient functioning as assessed by the Herpes Symptom Checklist Questionnaire (mean Herpes Symptom Checklist score over 5 days [possible total score from 0 to 39; lower score indicates less severe symptoms]: 4.77 with 2 days of famciclovir v 4.98 with 5 days of famciclovir; P = 0.40). The RCT included people with HIV if their CD4 count was 500 cells/microlitre or greater and/or CD4 cells 25% or greater of total lymphocytes within previous 3 months: 7.9% of recurrences in the group receiving famciclovir for 2 days and 10.1% of recurrences in the group receiving famciclovir for 5 days were in people who were HIV positive.

Valaciclovir for 3 days versus 5 days:
We found two RCTs. The first RCT (531 people with at least 6 recurrences of genital herpes a year) found no difference between 3 and 5 days of treatment with valaciclovir 500 mg twice daily in episode duration or aborted recurrences (median episode duration: 4.7 days with 3 days of valaciclovir v 4.6 days with 5 days of valaciclovir; significance not reported; aborted recurrences: 27% with 3 days of valaciclovir v 21% with 5 days of valaciclovir; RR 1.23, 95% CI 0.92 to 1.65). People initiating treatment within 6 hours of first symptoms or signs were significantly more likely to have an aborted episode than those starting treatment after 6 hours (OR 1.93, 95% CI 1.28 to 2.9). The second RCT (800 people with at least 4 outbreaks of genital herpes a year) found no significant difference between 3 and 5 days of treatment with valaciclovir (500 mg twice daily) in lesion healing time or aborted lesions (median healing time: 4.4 days with 3 days of valaciclovir v 4.7 days with 5 days of valaciclovir; HR 0.95, 95% CI 0.81 to 1.13; aborted lesions: 25% with 3 days of valaciclovir v 27% with 5 days of valaciclovir; RR 1.04, 95% CI 0.83 to 1.32).

Famciclovir versus placebo:
The review reported that adverse effects (mostly headache and nausea) were rare, and the frequency was similar for aciclovir, valaciclovir, famciclovir, and placebo (figures not reported in the review).

One subsequent RCT reported adverse effects of mild to moderate severity associated with famciclovir (mostly headache, nausea, diarrhoea, abdominal pain, and dizziness).

Famciclovir versus valaciclovir:
The RCT comparing famciclovir versus valaciclovir found a similar rate of overall adverse effects in each group (86/371 [23%] with famciclovir v 86/385 [22%] with valaciclovir; significance not assessed). The RCT reported that the most common adverse effects reported in either group were headache, nausea, and diarrhoea (headache: 29/371 [8%] with famciclovir v 17/385 [4%] with valaciclovir; nausea: 23/371 [6%] with famciclovir v 18/385 [5%] with valaciclovir; diarrhoea: 8/371 [2%] with famciclovir v 5/385 [1%] with valaciclovir; significance not assessed for any outcome). Grade 3 or grade 4 toxicity in haematological and serum chemistry laboratory values was also similar for famciclovir and valaciclovir (includes tests for hypoglycaemia, serum lipase, and amylase).
Famciclovir for 2 days versus 5 days:
The RCT comparing different durations of famciclovir reported that the proportion of people experiencing adverse effects was similar in the groups taking famciclovir for 2 days and for 5 days, with headache being the most common adverse effect reported (16% of recurrences with 2 days of famciclovir v 18% of recurrences with 5 days of famciclovir; significance not assessed; absolute numbers not reported). (56)

Comment:
In the past, there was some controversy regarding the biological and clinical meaning of asymptomatic HSV-2 infection. (46) However, a study by Wald et al in 2000 suggested that the pattern, sites, and frequency of subclinical reactivation of infection in people seropositive for HSV-2 was similar to that in people with symptomatic infection. (46) Therefore, people seropositive for HSV-2 are treated in the same way as those with recurrent symptomatic infection and we include both groups in this option.

Clinical guide:
The benefit was found to be greater if the person with recurrent herpes initiated treatment at the first symptom or sign of a recurrence, ideally within 6 hours of onset of symptoms. (51) (56) (58)

| OPTION | PSYCHOTHERAPY |
|--------|---------------|

Recurrence of infection
Compared with control Psychotherapy may reduce recurrence rates of genital herpes (very low-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.

Benefits:
We found one systematic review (search date 1991), which identified 6 poor-quality studies of psychotherapeutic interventions in 69 people (4 studies had <10 people). (59) Interventions varied from hypnotherapy and progressive muscle relaxation to cognitive therapy and multifaceted intervention. The largest RCT (31 people with >4 recurrences a year) compared psychosocial intervention versus social support or waiting list. (59) Psychosocial intervention involved information on herpes simplex virus (HSV), relaxation training, stress management instructions, and an imagery technique. People receiving social support discussed their feelings and experiences relating to HSV infection. People receiving psychosocial intervention had significantly lower recurrence rates compared with pretreatment frequency, social support, or waiting list (recurrences per year: 6 with psychosocial intervention v 11 [in total] with pretreatment, social support, and waiting list; P <0.001). However, small numbers of people, inadequate controls, and subjective and retrospective assessment of recurrence frequency at baseline limit the usefulness of these studies. (59)

Harms:
The review (59) and the RCT (60) gave no information on adverse effects.

Comment:
In the past, there was some controversy regarding the biological and clinical meaning of asymptomatic HSV-2 infection. (46) However, a study by Wald et al in 2000 suggested that the pattern, sites, and frequency of subclinical reactivation of infection in people seropositive for HSV-2 was similar to that in people with symptomatic infection. (46) Therefore, people seropositive for HSV-2 are treated in the same way as those with recurrent symptomatic infection and we include both groups in this option.

Controlled studies that include prospective clinical evaluation of disease activity are needed.

QUESTION What are the effects of treatments in people with genital herpes and HIV?

| OPTION | DAILY ORAL ANTIVIRAL TREATMENT FOR PREVENTING RECURRENCE OF GENITAL HERPES IN PEOPLE WITH HIV |
|--------|----------------------------------------------------------------------------------------|

Recurrence of infection
Aciclovir compared with placebo Aciclovir may be more effective at reducing recurrence of genital ulcer disease at 3 months in women with HIV (low-quality evidence).

Valaciclovir compared with placebo Valaciclovir is more effective at reducing recurrence of episodes of genital ulcers and increasing time to recurrence in people with HIV (moderate-quality evidence).

Valaciclovir compared with aciclovir Valaciclovir and aciclovir are equally effective at reducing recurrence of genital ulcers at 48 weeks in people with HIV (high-quality evidence).

Viral shedding
Aciclovir compared with placebo: Aciclovir seems more effective at reducing rate of HSV-2 shedding in women with HIV (moderate-quality evidence).

Valaciclovir compared with placebo: Valaciclovir seems more effective at reducing the proportion of women with HSV-2 shedding during 3 months’ treatment in women with HIV (moderate-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.

Benefits: Aciclovir versus placebo:

We found two RCTs comparing aciclovir versus placebo. [61] [62]

The first RCT (300 women who were seropositive for HIV and herpes simplex virus type 2 [HSV-2] and who were not receiving antiretroviral treatment) found that, compared with placebo, aciclovir (400 mg twice daily for 3 months) significantly reduced recurrence of genital ulceration during 3 months’ follow-up (proportion of women with at least 1 episode of genital ulcer disease: 11/146 [8%] with aciclovir vs 25/142 [18%] with placebo; RR 0.43, 95% CI 0.22 to 0.84; P = 0.01) and significantly reduced genital HSV-2 shedding at 3 months (proportion of women with detectable genital HSV-2 DNA at 3 months: 10/133 [8%] with aciclovir vs 28/137 [20%] with placebo; RR 0.37, 95% CI 0.19 to 0.73; P = 0.002). [61] Of the women enrolled, 97 women self-reported genital ulcer disease in the 3 months before enrolment (45/151 [30%] in the aciclovir group vs 52/148 [35%] in the placebo group).

The second RCT (214 women with HIV) compared aciclovir (400 mg twice daily for 12 weeks) versus placebo. [62] The RCT reported a subgroup analysis of women who were seropositive for HIV and HSV-2 (125 women; 69 women in the aciclovir group and 56 women in the placebo group). The RCT found that aciclovir significantly reduced HSV-2 shedding compared with placebo (HSV-2 shedding expressed as number of women with detectable HSV-2 DNA out of sum of women attending designated follow-up visits over 3 months: 64/646 [10%] with aciclovir vs 123/551 [23%] with placebo; OR 0.24, 95% CI 0.12 to 0.50; P <0.001). [62] The RCT reported that a larger proportion of women were shedding HSV-2 at baseline in the aciclovir group compared with the placebo group, but the difference was not statistically significant (20/69 [29%] with aciclovir vs 9/56 [16%] with placebo; reported as not significant; P value not reported). The RCT reported that no women in either group were observed to have recurrent symptomatic genital ulceration during 3 months’ follow-up. The RCT had lower power to detect differences in HIV shedding than initially planned by the authors.

Valaciclovir versus placebo:

We found three RCTs comparing valaciclovir versus placebo. [63] [64] [65]

The first RCT (239 people with HIV and a history of symptomatic recurrent genital herpes) found that valaciclovir (500 mg twice daily) significantly reduced recurrence at 6 months (AR for freedom from recurrence: 65% with valaciclovir vs 26% with placebo; RR 2.5, 95% CI 1.8 to 3.5; absolute numbers not reported) and increased the median time to first recurrence (>180 days with valaciclovir vs 59 days with placebo; HR 16.7, 95% CI 7.3 to 33.3) compared with placebo. [65]

The second RCT (60 women with HIV receiving antiretroviral treatment and with serological evidence of HSV-2 antibodies) found no significant difference between valaciclovir (500 mg twice daily) for 3 months and placebo in the proportion of women with at least one clinical ulcer episode during 3 months’ follow-up (defined as 1 episode of genital ulcer or blister in the genital area; 0/30 [0%] with valaciclovir vs 2/30 [3%] with placebo; P = 0.99). [64] The RCT also found no significant difference between groups in the proportion of women recorded as shedding genital HSV-2 DNA at least once during 3 months’ treatment (9/30 [30%] with valaciclovir vs 13/30 [43%] with placebo; RR 0.66, 95% CI 0.33 to 1.31; P = 0.24).

The third RCT (140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies) found that, compared with placebo, valaciclovir (500 mg twice daily) for 3 months significantly reduced recurrence of genital ulceration at 3 months (defined as at least 1 episode of vesicle or genital ulceration; 3/68 [5%] with valaciclovir vs 19/68 [28%] with placebo; RR 0.16, 95% CI 0.05 to 0.51; P = 0.002) and significantly reduced HSV-2 shedding at 3 months (proportion of women recorded as shedding genital HSV-2 DNA at least once during 3 months’ treatment: 13/68 [19%] with valaciclovir vs 37/68 [54%] with placebo; RR 0.33, 95% CI 0.20 to 0.60; P <0.001). [65]

Valaciclovir versus aciclovir:

We found one RCT (1062 people), which compared three treatments: valaciclovir 500 mg twice daily, aciclovir 1000 mg once daily, and aciclovir 400 mg twice daily for 48 weeks. [66] It found no significant difference between either dose of valaciclovir and aciclovir in time to recurrence (HR...
for valaciclovir 500 mg twice daily v aciclovir 0.73, 95% CI 0.50 to 1.06; HR for valaciclovir 1000 mg once daily v aciclovir 1.31, 95% CI 0.94 to 1.82).

**Harms:**

**Aciclovir versus placebo:**
The RCTs gave no information on adverse effects. [61] [62]

**Valaciclovir versus placebo:**
The first RCT found that valaciclovir increased the risk of headache, fatigue, influenza, nasopharyngitis, and rash compared with placebo (headache: 13% with valaciclovir v 8% with placebo; fatigue: 8% with valaciclovir v 5% with placebo; influenza: 8% with valaciclovir v 3% with placebo; nasopharyngitis: 8% with valaciclovir v 2% with placebo; rash: 8% with valaciclovir v 1% with placebo). Rates of diarrhoea and nausea were similar between treatments (diarrhoea: 12% with both treatments; nausea: 8% with both treatments). [63] The RCT gave no information on adverse effects in people taking valaciclovir beyond 6 months.

The second RCT gave no information on adverse effects. [64]

The third RCT found no significant difference between valaciclovir and placebo in headache, fatigue, nausea, vomiting, diarrhoea, constipation, and hypersensitivity reactions (headache: 20/68 [29%] with valaciclovir v 27/68 [40%] with placebo; P = 0.21; fatigue: 10/68 [15%] with valaciclovir v 17/68 [25%] with placebo; P = 0.13; nausea: 11/68 [16%] with valaciclovir v 7/68 [10%] with placebo; P = 0.31; vomiting: 4/68 [6%] with valaciclovir v 6/68 [9%] with placebo; P = 0.51; diarrhoea: 3/68 [4%] with valaciclovir v 7/68 [10%] with placebo; P = 0.19; constipation: 5/68 [7%] with valaciclovir v 10/68 [15%] with placebo; P = 0.17; hypersensitivity reactions: 10/68 [15%] with valaciclovir v 14/68 [21%] with placebo; P = 0.37). [65]

**Valaciclovir versus aciclovir:**
The RCT found that the rate of withdrawal because of adverse effects was similar with aciclovir and valaciclovir (AR adverse effects leading to withdrawal, including nausea and headache: 11% with valaciclovir v 9% with aciclovir; significance not assessed). [66]

**Comment:**
Valaciclovir significantly reduced the rate of recurrences of genital herpes. However, 35% of people being treated had a recurrence within 6 months. [63] One RCT found that recurrence was significantly more likely with valaciclovir 1000 mg taken once daily than with valaciclovir 500 mg taken twice daily (people remaining recurrence free at 48 weeks: 71% with valaciclovir 1000 mg once daily v 82% with valaciclovir 500 mg twice daily; HR 1.80, 95% CI 1.26 to 2.57; P <0.05). [66]

In the past, there was some controversy regarding the biological and clinical meaning of asymptomatic HSV-2 infection. [66] However, a study by Wald et al in 2000 suggested that the pattern, sites, and frequency of subclinical reactivation of infection in people seropositive for HSV-2 was similar to that in people with symptomatic infection. [26] Therefore, people seropositive for HSV-2 are treated in the same way as those with recurrent symptomatic infection and we include both groups in this option.

**Clinical guide**
Epidemiological and laboratory data suggest that genital HSV-2 infection increases the infectiousness of people with HIV-1 infection. Data from RCTs show that daily treatment for HSV-2 reduces plasma HIV RNA levels. These results suggest that suppression may be beneficial to reduce the transmission rate of HIV. However, one large RCT of suppressive aciclovir (400 mg twice daily) given for up to 24 months to people who were infected with both HIV-1 and HSV-2 and who had CD4 counts of >250 cells per mm$^3$, did not reduce transmission of HIV-1 to sexual partners, despite significant reductions in plasma HIV-1 concentrations and in the incidence of genital ulcer disease caused by HSV-2. [11]

**OPTION**

**ANTIVIRAL TREATMENT (ORAL) FOR FIRST EPISODE OF GENITAL HERPES IN PEOPLE WITH HIV**

We found no clinically important results from RCTs about the effects of treatment of first-episode genital herpes in people with HIV.

**Note**
Current consensus is that oral antiviral treatment is effective for the treatment of first-episode genital herpes in people with HIV.

For GRADE evaluation of interventions for genital herpes, see table, p 24.
Benefits: We found no systematic review or RCTs examining effects of treatments for the first episode of genital herpes in people with HIV.

Harms: We found no RCTs.

Comment: Clinical guide
Current consensus is that oral antiviral treatment is effective for the treatment of first-episode genital herpes in people with HIV.

OPTION
ANTIVIRAL TREATMENT (ORAL) VERSUS NO TREATMENT FOR AN ACUTE RECURRENT EPISODE OF GENITAL HERPES IN PEOPLE WITH HIV

Severity of attack
Compared with placebo Aciclovir, when given as part of syndromic management of genital ulcer disease, may be more effective at increasing healing rate at 7 days and reducing time to healing in HIV-positive men and women with an acute recurrent episode of genital herpes (low-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.

Benefits: Aciclovir versus placebo:
We found two RCTs comparing aciclovir versus placebo in people with HIV and testing seropositive for herpes simplex virus type 2 (HSV-2). [67] [68]

The first RCT (615 men with a genital ulcer) compared oral aciclovir 400 mg (3 times daily for 5 days) versus placebo. [67] All men also received antibiotics (benzathine benzylpenicillin intramuscularly plus oral ciprofloxacin) for syndromic management of genital ulcers. The RCT reported a subgroup analysis of men who were HIV positive and had a herpetic ulcer (295 HSV-2 seropositive and HIV-positive men; 146 men in the aciclovir group and 149 men in the placebo group): the RCT included men who reported not having previous sores in the genital area (proportion of men reporting a previous sore in the genital area: 82/146 [58%] in the aciclovir group v 92/149 [63%] in the placebo group). The RCT found that aciclovir significantly increased healing rate at 7 days compared with placebo (proportion of men with healed lesions at 7 days: 80/132 [61%] with aciclovir v 59/139 [42%] with placebo; RR 1.4, 95% CI 1.1 to 1.8) and significantly reduced median time to healing (self-reported healing: 6 days with aciclovir v 9 days with placebo; P = 0.002).

The second RCT (441 women with genital ulcers) compared oral aciclovir 400 mg (3 times daily for 5 days) versus placebo. All women also received antibiotics (benzathine penicillin intramuscularly plus oral ciprofloxacin) for syndromic management of genital ulcers. The RCT reported a subgroup analysis of women who were HIV-positive and had a herpetic ulcer (118 HSV-2 seropositive and HIV-positive women; 54 women in the aciclovir group and 64 women in the placebo group). Of the women included just over 40% had reported having genital ulcers in the previous year (25/54 [47%] of women receiving aciclovir v 27/64 [42%] of women receiving placebo). [68] The RCT found no significant difference between aciclovir and placebo in rate of healing at 7 days (proportion of women with healed lesions [greater than or equal to90% reduction in ulcer size] at 7 days: 26/47 [55%] with aciclovir v 26/59 [44%] with placebo; RR 1.26, 95% CI 0.9 to 1.9), although the proportion of women with healed lesions was larger with aciclovir. The RCT may have been underpowered to detect a clinically important difference between groups.

Harms: Aciclovir versus placebo:
The RCTs gave no information on adverse effects. [67] [68]

Comment:
In the past, there was some controversy regarding the biological and clinical meaning of asymptomatic HSV-2 infection. [46] However, a study by Wald et al in 2000 suggested that the pattern, sites, and frequency of subclinical reactivation of infection in people seropositive for HSV-2 was similar to that in people with symptomatic infection. [46] Therefore, people seropositive for HSV-2 are treated in the same way as those with recurrent symptomatic infection and we include both groups in this option.

One prospective study found an increased rate of HSV shedding in people infected with HIV. [69] HIV has also been detected in genital herpes lesions, suggesting that HSV infection may increase the risk of sexual transmission of HIV. [70]

Clinical guide:
In countries in which HSV is the predominant genital ulcer disease (GUD) aetiology, the World Health Organization recommends that a treatment programme should include antiviral episodic treatment as part of GUD syndromic management. [71]
Severity of attack
Antiviral drugs compared with each other Aciclovir is as effective as famciclovir or valaciclovir at reducing the duration of symptoms in people with HIV who have acute recurrent episodes of genital herpes (high-quality evidence).

Viral shedding
Antiviral drugs compared with each other Aciclovir and famciclovir seem equally effective at reducing the duration of viral shedding in people with HIV who have acute recurrent episodes of genital herpes (moderate-quality evidence).

For GRADE evaluation of interventions for genital herpes, see table, p 24.

Benefits: Antiviral drugs versus each other:
Famciclovir versus aciclovir:
We found one RCT (193 people on stable antiretroviral treatment), which compared famciclovir (500 mg twice daily) versus aciclovir (400 mg 5 times daily) for 1 week. It found no significant difference between treatments in time to healing, duration of viral shedding, or time to loss of symptoms (median time to healing: 7 days with both treatments; HR 1.01, 95% CI 0.79 to 1.29; median duration of viral shedding: 2 days with both treatments; HR 0.93, 95% CI 0.68 to 1.27; median time to loss of symptoms: 4 days with both treatments; HR 0.99, 95% CI 0.75 to 1.30). It also found no significant difference between the two treatments in the risk of developing new lesions during treatment (17% with famciclovir v 13% with aciclovir; ARI +3.4%, 95% CI –4.8% to +11.5%).

Valaciclovir versus aciclovir:
We found one RCT (467 people), which compared valaciclovir (1000 mg twice daily) versus aciclovir (200 mg 5 times daily) for 5 days. It found no significant difference between treatments in time to lesion healing or episode duration (time to lesion healing: HR 0.98, 95% CI 0.79 to 1.22; episode duration: HR 0.93, 95% CI 0.75 to 1.14).

Harms: Antiviral drugs versus each other:
Famciclovir versus aciclovir:
The RCT reported that adverse effects, mostly headache, nausea, diarrhoea, and abdominal pain, were experienced by >3% of people taking either famciclovir or aciclovir(headache: 17% with famciclovir v 15% with aciclovir; nausea: 11% with famciclovir v 13% with aciclovir; diarrhoea: 7% with famciclovir v 11% with aciclovir; abdominal pain: 3% with famciclovir v 6% with aciclovir; significance not assessed). There were no reports of either haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura.

Valaciclovir versus aciclovir:
The RCT reported that adverse effects, mostly headache, nausea, and diarrhoea, were experienced by fewer than 10% of people taking either valaciclovir or aciclovir.

Comment: None.

GLOSSARY
Serodiscordant couple A couple in which one partner is infected with herpes simplex virus and the other is not infected.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES
Antiviral maintenance treatment (oral) in late pregnancy (at least 36 weeks' gestation) in women with a history of genital herpes New evidence added. Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge whether antivirals reduce the rate of transmission of infection because of the rarity of neonatal transmission of herpes simplex virus (HSV) from women with recurrent genital herpes.

Daily antiviral maintenance treatment for preventing recurrence of genital herpes in people with HIV New evidence added. Categorisation changed from Likely to be beneficial to Beneficial.
Daily oral antiviral treatment (reducing the impact of recurrence) New evidence added; [11]  [36]  [42]  [43] categorisation unchanged (Beneficial).

Oral antiviral treatment taken at the start of recurrence New evidence added; [53]  [54]  [55] categorisation unchanged (Beneficial).

Antiviral treatment (oral) versus no treatment for an acute recurrent episode of genital herpes in people with HIV Two RCTs added; [67]  [69] categorisation changed from Likely to be beneficial by consensus to Likely to be beneficial (based on RCT evidence).

Male condom use to prevent sexual transmission from infected women to uninfected men Evidence reassessed. Categorisation changed from Unknown effectiveness to Likely to be beneficial by consensus.

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### GRADE evaluation of interventions for genital herpes

| Number of studies (participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
|----------------------------------|---------|------------|------------------|---------|-------------|------------|-------------|--------|---------|
| **What are the effects of interventions to prevent sexual transmission of herpes simplex virus?** | | | | | | | | | |
| 1 (1484) [15] | Transmission of infection | Antiviral drugs v placebo | 4 | 0 | 0 | −1 | 0 | Moderate | Directness point deducted for narrow range of interventions studied |
| 1 (528) [17] | Transmission of infection | Male condoms v no condoms (male partner infected) | 2 | 0 | 0 | −1 | +2 | Moderate | Directness point deducted for poor use of condoms. Effect-size points added for RR <0.2 |
| 1 (528) [17] | Transmission of infection | Male condom use v no condoms (female partner infected) | 2 | 0 | 0 | −1 | 0 | Very low | Directness point deducted for poor use of condoms |
| 2 (5107) [21] [22] | Transmission of infection | Recombinant glycoprotein vaccines v placebo | 4 | 0 | −1 | 0 | 0 | Moderate | Consistency point deducted for conflicting results |
| **What are the effects of interventions to prevent transmission of herpes simplex virus from mother to neonate?** | | | | | | | | | |
| 7 (1249) [26] | Transmission of infection | Oral antivirals v placebo | 4 | 0 | 0 | −1 | 0 | Moderate | Directness point deducted for no events in either group |
| 7 (1249) [26] | Recurrence of infection | Oral antivirals v placebo | 4 | 0 | 0 | 0 | +1 | High | Effect-size point added for RR <0.5 |
| 7 (1249) [26] | Caesarean section rate | Oral antivirals v placebo | 4 | 0 | 0 | −1 | +1 | High | Directness point deducted for potential variation in when caesarean section was performed. Effect-size point added for RR <0.5 |
| **What are the effects of antiviral treatment in people with a first episode of genital herpes?** | | | | | | | | | |
| 3 (259) [32] [33] [34] | Severity of attack | Oral aciclovir v placebo | 4 | −1 | 0 | 0 | 0 | Moderate | Quality point deducted for methodological flaws |
| 3 (259) [32] [33] [34] | Viral shedding | Oral aciclovir v placebo | 4 | −1 | 0 | 0 | 0 | Moderate | Quality point deducted for methodological flaws |
| 1 (643) [35] | Severity of attack | Valaciclovir v aciclovir | 4 | 0 | 0 | 0 | 0 | High | |
| 1 (643) [35] | Viral shedding | Valaciclovir v aciclovir | 4 | 0 | 0 | 0 | 0 | High | |
| **What are the effects of interventions to reduce the impact of recurrence?** | | | | | | | | | |
| 14 (6292) [36] | Recurrence of infection | Antivirals v placebo (maintenance treatment) | 4 | −1 | 0 | 0 | 0 | Moderate | Quality point deducted for statistical heterogeneity among RCTs |
| 12 (6500) [11] [37] | Recurrence of infection | Aciclovir v placebo (maintenance treatment) | 4 | 0 | 0 | 0 | 0 | High | |
| 1 (34) [38] | Viral shedding | Aciclovir v placebo (maintenance treatment) | 4 | −1 | 0 | −1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for narrowness of population (women with duration of infection of <2 years) |
| 1 (369) [39] | Quality of life | Aciclovir v placebo (maintenance treatment) | 4 | 0 | 0 | 0 | 0 | High | |
| Number of studies (participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
|---------------------------------|---------|------------|-----------------|--------|-------------|------------|------------|--------|---------|
| 3 (1004) [36] [41] | Recurrence of infection | Famciclovir v placebo (maintenance treatment) | 4 | –2 | +1 | 0 | 0 | Moderate | Quality points deducted for statistical heterogeneity between RCTs and for no pre-crossover results in 1 RCT. Consistency point added for dose response |
| 1 (114) [41] | Viral shedding | Famciclovir v placebo (maintenance treatment) | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for sparse data, no pre-crossover results, and for no statistical assessment of between-group difference |
| 5 (3305) [36] [42] [43] | Recurrence of infection | Valaciclovir v placebo (maintenance treatment) | 4 | –1 | +1 | 0 | 0 | High | Quality point deducted for statistical heterogeneity among RCTs in meta-analysis. Consistency point added for evidence of dose response |
| 1 (152) [42] | Viral shedding | Valaciclovir v placebo (maintenance treatment) | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |
| 1 (1106) [39] | Quality of life | Valaciclovir v placebo (maintenance treatment) | 4 | 0 | 0 | 0 | 0 | High | |
| 1 (320) [44] | Recurrence of infection | Famciclovir v valaciclovir (maintenance treatment) | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 1 (70) [44] | Viral shedding | Famciclovir v valaciclovir (maintenance treatment) | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |
| At least 2 (781) [47] | Severity of attack | Aciclovir v placebo (treatment initiated at start of recurrence) | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| At least 2 (781) [47] | Viral shedding | Aciclovir v placebo (treatment initiated at start of recurrence) | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 3 (1104) [49] [50] [51] | Severity of attack | Famciclovir v placebo (treatment initiated at start of recurrence) | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 2 (775) [49] [50] | Viral shedding | Famciclovir v placebo (treatment initiated at start of recurrence) | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 1 (987) [49] | Severity of attack | Valaciclovir v placebo (treatment initiated at start of recurrence) | 4 | 0 | 0 | 0 | 0 | High | |
| 1 (987) [49] | Viral shedding | Valaciclovir v placebo (treatment initiated at start of recurrence) | 4 | 0 | 0 | 0 | +1 | High | Effect size point added for HR >2 |
| 1 (204) [52] | Severity of attack | Famciclovir v aciclovir (treatment initiated at start of recurrence) | 4 | 0 | 0 | 0 | 0 | High | |
| 1 (751) [53] | Severity of attack | Famciclovir v valaciclovir (treatment initiated at start of recurrence) | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for no significance assessment of between-group difference for aborted lesions |
| 1 (739) [49] | Severity of attack | Valaciclovir v aciclovir (treatment initiated at start of recurrence) | 4 | 0 | 0 | 0 | 0 | High | |
| 1 (739) [49] | Viral shedding | Valaciclovir v aciclovir (treatment initiated at start of recurrence) | 4 | 0 | 0 | 0 | 0 | High | |
| Number of studies (participants) | Outcome                          | Comparison                                           | Type of evidence | Consistency | Directness | Effect size | GRADE   | Comment                                                                 |
|---------------------------------|----------------------------------|------------------------------------------------------|------------------|-------------|------------|-------------|----------|-------------------------------------------------------------------------|
| 1 (1024 recurrences) [55]       | Severity of attack               | Famciclovir 2 days v 5 days (treatment initiated at start of recurrence) | 4                | -1          | 0          | 0           | 0        | Moderate Quality point deducted for incomplete reporting of results   |
| 2 (1331) [56] [57]              | Severity of attack               | Valaciclovir 3 days v 5 days (treatment initiated at start of recurrence) | 4                | -1          | 0          | 0           | 0        | Moderate Quality point deducted for incomplete reporting of results   |
| 6 (69) [58]                     | Recurrence of infection          | Psychotherapy v control                              | 4                | -3          | 0          | -1          | 0        | Very low Quality points deducted for sparse data, inadequate controls, and flawed assessment of outcomes. Directness point deducted for wide range of comparators |
|                                 |                                  |                                                      |                  |             |            |             |          |                                                                         |
|                                 | What are the effects of treatments in people with genital herpes and HIV? |                                                      |                  |             |            |             |          |                                                                         |
| 2 (425) [61] [62]               | Recurrence of infection          | Aciclovir v placebo (preventing recurrence)          | 4                | -2          | 0          | 0           | 0        | Low Quality points deducted for subgroup analysis in 1 RCT and for 1 RCT being underpowered to detect a clinically important difference between groups |
| 2 (425) [61] [62]               | Viral shedding                   | Aciclovir v placebo (preventing recurrence)          | 4                | -2          | 0          | 0           | +1       | Moderate Quality points deducted for subgroup analysis in 1 RCT and for 1 RCT being underpowered to detect a clinically important difference between groups |
| 3 (435) [63] [64] [65]          | Recurrence of infection          | Valaciclovir v placebo (preventing recurrence)       | 4                | -1          | 0          | 0           | 0        | Moderate Quality point deducted for incomplete reporting of results in largest RCT |
| 2 (196) [64] [65]               | Viral shedding                   | Valaciclovir v placebo (preventing recurrence)       | 4                | -1          | 0          | 0           | 0        | Moderate Quality point deducted for sparse data                          |
| 1 (1062) [66]                   | Recurrence of infection          | Valaciclovir v aciclovir (preventing recurrence)      | 4                | 0           | 0          | 0           | 0        | High Quality points deducted for subgroups analyses in both RCTs and for 1 RCT being underpowered to detect a clinically important difference between groups |
| 2 (377) [67] [68]               | Severity of attack               | Aciclovir v placebo (treatment of an acute recurrent episode) | 4                | -2          | 0          | 0           | 0        | Low Quality point deducted for sparse data                               |
| 2 (660) [66] [72]               | Severity of attack               | Antiviral agents v each other (treatment of an acute recurrent episode) | 4                | 0           | 0          | 0           | 0        | High Quality point deducted for sparse data                               |
| 1 (193) [72]                    | Viral shedding                   | Antiviral agents v each other (treatment of an acute recurrent episode) | 4                | -1          | 0          | 0           | 0        | Moderate Quality point deducted for sparse data                           |

Type of evidence: 4 = RCT; 2 = Observational. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. Effect size: based on relative risk or odds ratio.