ClinicalEvidence

Genital herpes: oral antiviral treatments

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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. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of different oral antiviral treatments versus each other for a first episode of genital herpes in HIV-negative people? What are the effects of different antiviral treatments for genital herpes in HIV-positive people? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2013 (BMJ 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 eight 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: aciclovir, famciclovir, and valaciclovir.

QUESTIONS

What are the effects of different oral antiviral treatments versus each other for a first episode of genital herpes in HIV-negative people? 4

What are the effects of different oral antiviral treatments for genital herpes in HIV-positive people? 6

INTERVENTIONS

TREATMENTS FOR A FIRST EPISODE IN HIV-NEGATIVE PEOPLE

Unknown effectiveness

Oral antiviral treatments (aciclovir, valaciclovir, famciclovir) versus each other for treatment of a first episode of genital herpes in HIV-negative people (oral valaciclovir and oral acyclovir are equally effective in treating a first episode of genital herpes in HIV negative people) . . 4

TREATING PEOPLE WITH HIV

Beneficial

Daily oral antiviral treatment (aciclovir, valaciclovir, famciclovir) for preventing recurrence of genital herpes in HIV-positive people 6

Unknown effectiveness

Oral antiviral treatments (aciclovir, famciclovir, valaciclovir) versus each other for first episodes of genital herpes in HIV-positive people 14

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 a first episode of genital herpes can decrease symptoms in HIV-negative people.

  Data from one RCT indicated that oral valaciclovir and oral aciclovir were equally effective in treating a first episode of genital herpes in HIV-negative people.

  We found no RCTs of sufficient quality comparing either oral valaciclovir or oral aciclovir with oral famciclovir in treating a first episode of genital herpes in HIV-negative people.

- Daily oral antiviral treatment seems to be effective in preventing recurrence of genital herpes in HIV-positive people.

  Data from one RCT indicated that daily oral valaciclovir and daily oral aciclovir seemed equally effective in preventing recurrence of genital herpes in HIV-positive people.

  We found no RCTs of sufficient quality comparing either oral valaciclovir or oral aciclovir with oral famciclovir in preventing recurrence of genital herpes in HIV-positive people.

- We found no RCTs of sufficient quality to assess whether one oral antiviral is more effective than another in treating first episodes of genital herpes in HIV-positive people.

Clinical context

GENERAL BACKGROUND

Genital herpes simplex infection can be caused by either herpes simplex virus (HSV) type 1 (HSV-1) or HSV type 2 (HSV-2) and is one of the most common sexually transmitted diseases. Common symptoms include recurrent painful genital ulcerations. Asymptomatic shedding is frequent, especially in the first year after a primary episode, and probably represents the major source of sexual transmission. The herpes virus has a characteristic protein coat and each of the types has identifiable proteins. Glycoprotein G2 is associated with HSV-2 and glycoprotein G1 is associated with HSV-1 Type-specific antibodies to the viral proteins develop within the first several weeks of infection and persist. Detection of these specific antibodies, in addition to direct detection of the virus, is important in making an accurate diagnosis. There is no cure for HSV infection. In repeated randomised clinical trials, the use of antiviral agents compared to placebo for individuals with a first episode of genital HSV significantly reduces the duration of symptoms and speeds healing. The use of antiviral medications is also shown to reduce the frequency and duration of recurrent outbreaks and to reduce the frequency of asymptomatic shedding. Oral antiviral treatment of someone who is seropositive for HSV is effective in reducing transmission to a previously uninfected sexual partner. 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.

FOCUS OF THE REVIEW

This update to a previously published review focuses on specific questions for which evidence was insufficient to identify the best treatment. There is now a preponderance of evidence supporting the role of antiviral treatment in treatment of the initial episode of genital herpes. However selecting the most appropriate antiviral treatment remains a challenge and, therefore, this review focuses on the effects of different oral antiviral treatments in two select populations: HIV-negative individuals with a first episode of genital herpes and treatment of both first episode and recurrences for HIV-positive individuals. These populations were selected because evidence from clinical trials was limited at the time of the last systematic review, and an update in these areas could provide clinicians with information on best therapies.

COMMENTS ON EVIDENCE

We found eight studies that met our inclusion criteria. In regards to the question of the effects of different oral antiviral treatments versus each other for a first episode of genital herpes in the HIV-negative individual, we found high grade evidence from one randomised controlled trial comparing oral valaciclovir and acyclovir. Both treatments were equally effective in treating the first episode by decreasing symptoms with similar rates of adverse effects; however, this evidence is from a single study. For the question regarding treatment of recurrent infections in HIV-positive individuals, we found moderate to very low grade evidence from seven trials. Studies for HIV positive individuals were only included if the majority of subjects in the study were HIV positive. In particular, we found moderate evidence that the recurrence rates of HSV are lower for HIV-positive individuals on valaciclovir compared to placebo, and the recurrence rates are similar between those on acyclovir when compared to valaciclovir. While studies indicated that HIV-positive individuals on acyclovir as compared to placebo had lower recurrence rates and less viral shedding, these studies had several methodological issues.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, January 2010, to October 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 62 studies. After deduplication and removal of conference abstracts, 48 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 28 studies and the further review of 20 full publications. Of the 20 full articles evaluated, no systematic reviews and one RCT was added at this update.

ADDITIONAL INFORMATION

In this review we found no randomised controlled trials of sufficient quality comparing famciclovir with other antiviral therapies. Famciclovir is an oral pro-drug of penciclovir with increased bio-availability and a longer half-life than acyclovir and, therefore, is considered a treatment option for primary genital herpes outbreak. There are studies comparing famciclovir with placebo, showing favourable results.

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 (e.g., polymerase chain reaction) 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). Genital herpes can be diagnosed using various methods (e.g., clinical diagnosis, culture or PCR of lesions, or serological testing). Clinical diagnosis alone has been shown to be both insensitive and non-specific, therefore, guidelines recommend that evaluation for genital, anal, or perianal ulcers include syphilis serology and darkfield examination, culture for HSV or PCR testing for HSV, and serological testing for type-specific HSV antibody. [1]

INCIDENCE/ PREVALENCE

Genital herpes infections are among the most common sexually transmitted diseases. Seroprevalence studies showed that 17% of adults in the US, [2] 9% of adults in Poland, [3] and 12% of adults in Australia [4] had HSV-2 antibodies. The studies carried out in Poland and Australia also showed higher seroprevalence in women than in men (HSV-2 seroprevalence in Poland: 10% for women *v* 9% for men; P = 0.06; HSV-2 seroprevalence in Australia: 16% for women *v* 9% for men; RR 1.81, 95% CI 1.52 to 2.14). A UK study found that 23% of adults attending sexual health clinics, and 8% of blood donors in London, had antibodies to HSV-2. [5] On the basis of seroprevalence studies, the total number of people who were newly infected with HSV-2 in 2003 has been estimated at 23.6 million, and the total number of people aged 15 to 49 years who were living with HSV-2 infection worldwide in 2003 has been estimated at 536 million. [6]

AETIOLOGY/ RISK FACTORS

Both HSV-1 and HSV-2 can cause genital infection, but HSV-2 is associated with a higher frequency of recurrences. [7] Most individuals with genital HSV infection have only mild symptoms and remain unaware that they have genital herpes. However, these people can still transmit the infection to sexual partners and newborns. [8] [9]

PROGNOSIS

Sequelae of HSV infection include neonatal HSV infection, opportunistic infection in immunocompromised people, recurrent genital ulceration, and psychosocial morbidity. HSV-2 infection is associated with an increased risk of HIV transmission and acquisition. [10] In a large meta-analysis of longitudinal studies in which the relative timing of HSV-2 infection and HIV infection could be established, HSV-2 seropositivity was a significant risk factor for HIV acquisition in general population studies of men (summary adjusted RR 2.7, 95% CI 1.9 to 3.9), women (RR 3.1, 95% CI 1.7 to 5.6), and men who had sex with men (RR 1.7, 95% CI 1.2 to 2.4). [11] Aciclovir suppressive therapy did not seem to reduce the rate of HIV infection in two RCTs that assessed this question. [12] [13] The first RCT (821 HIV-negative, HSV-2-seropositive women) found no significant difference between aciclovir (400 mg twice-daily) and placebo in the incidence of HIV infection (incidence of HIV infection: 4.4 per 100 person-years with aciclovir *v* 4.1 per 100 person-years with placebo; RR 1.08, 95% CI 0.64 to 1.83). [13] The second RCT (3172 HIV-negative, HSV-2-seropositive people) also found no significant difference between aciclovir (400 mg twice-daily) and placebo in the incidence of HIV infection (3.9 per 100 person-years with aciclovir *v* 3.3 per 100 person-years with placebo; HR 1.16, 95% CI 0.83 to 1.62). [12] Among the sequelae of HSV infection, the most common neurological complications are aseptic meningitis (reported in about 25% of women during primary infection) and urinary retention (reported in up to 15% of women during primary infection). [9] The absolute risk of neonatal infection is high (41%, 95% CI 26% to 56%) in babies born to women who acquire infection near the time of delivery, and low (<3%) in women with established infection, even in those who have a recurrence at delivery. [14] [15] About 15% of neonatal infections result from postnatal transmission from oral lesions of relatives or hospital personnel. [9]

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.

OUTCOMES

Transmission of infection (shown clinically, virologically, or serologically, depending on the study); **rate of seroconversion**; **severity of attack** (includes symptom severity and duration of lesions); **viral shedding** (an intermediate outcome that reflects the risk of transmitting the infection, although a direct link between the duration of viral shedding and risk of transmission has not been found); **recurrence rates**; **psychosocial morbidity**; **quality of life**; and **adverse effects**.

METHODS

BMJ Clinical Evidence search and appraisal October 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to October 2013, Embase 1980 to October 2013, and The Cochrane Database of Systematic Reviews 2013, issue 10 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts of the studies identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full

texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language that were single-blinded. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. RCTs consisted of 20 or more individuals (or at least 10 per arm), of whom at least 80% were followed up. We excluded all studies that recruited people with only a clinical diagnosis of genital herpes (i.e., without serological confirmation). For the question on HIV-positive people, we included studies with a mixed HIV population if the majority of the population was HIV positive. We excluded altogether from the review all studies with a mixed HIV population in which HIV-positive people were a minority. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. 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 17). The categorisation of the quality of the evidence (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 different oral antiviral treatments versus each other for a first episode of genital herpes in HIV-negative people?**

OPTION **ORAL ANTIVIRAL TREATMENTS (ACICLOVIR, VALACICLOVIR, FAMCICLOVIR) VERSUS EACH OTHER FOR TREATMENT OF A FIRST EPISODE OF GENITAL HERPES IN HIV-NEGATIVE PEOPLE**

- For GRADE evaluation of interventions for Genital herpes: oral antiviral treatments, see table, p 17 .
- Oral antiviral treatment of a first episode of genital herpes can decrease symptoms in HIV-negative people.
- Oral valaciclovir and oral aciclovir are equally effective in treating a first episode of genital herpes in HIV-negative people, but this is based on one RCT.
- Oral valaciclovir and oral aciclovir have similar rates of nausea and headache, when used to treat a first episode of genital herpes in HIV-negative people.
- We found no RCTs of sufficient quality comparing either oral valaciclovir or oral aciclovir with oral famciclovir in treating a first episode of genital herpes in HIV-negative people.

Benefits and harms

Oral valaciclovir versus oral aciclovir:

We found one RCT (643 people with first-episode genital herpes and HIV-negative) comparing oral valaciclovir (dosed twice-daily) versus oral aciclovir (dosed 5 times daily) given for 10 days. [16]

Severity of attack

Oral valaciclovir compared with oral aciclovir Oral valaciclovir and oral aciclovir are equally effective at reducing time to healing and reducing time to resolution of all symptoms for first episodes of genital herpes in HIV-negative people (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of attack					
[16] RCT	643 people with first episode genital herpes and HIV negative	**Median time to healing , days** 9 days with valaciclovir 9 days with aciclovir	HR 1.08 95% CI 0.92 to 1.27 P = 0.35	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] RCT	643 people with first episode genital herpes and HIV negative	**Median time to resolution of all symptoms , days** 9 days with valaciclovir 9 days with aciclovir	HR 1.02 95% CI 0.85 to 1.22 P = 0.85	⟷	Not significant

Viral shedding

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Viral shedding					
[16] RCT	643 people with first episode genital herpes and HIV negative	**Median duration of viral shedding , days** 3 days with valaciclovir 3 days with aciclovir	HR 1.00 95% CI 0.84 to 1.18 P = 0.99	⟷	Not significant

Transmission of infection

No data from the following reference on this outcome. [16]

Rate of seroconversion

No data from the following reference on this outcome. [16]

Recurrence rates

No data from the following reference on this outcome. [16]

Psychosocial morbidity

No data from the following reference on this outcome. [16]

Quality of life

No data from the following reference on this outcome. [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] RCT	643 people with first episode genital herpes and HIV negative	**Number of people reporting headache** 41/74 (55%) with oral valaciclovir 33/74 (45%) with oral aciclovir Headache was reported in a total of 74/643 (12%) of people	Reported as not significant P value not reported	⟷	Not significant
[16] RCT	643 people with first episode genital herpes and HIV negative	**Number of people reporting nausea** 18/38 (47%) with oral valaciclovir 20/38 (53%) with oral aciclovir Nausea was reported in a total of 38/643 (6%) of people	Reported as not significant P value not reported	⟷	Not significant

Comment:

Famciclovir is considered a treatment option for primary genital herpes outbreak. Famciclovir is an oral prodrug of penciclovir and has increased bio-availability and a longer half-life than aciclovir. [17] We found no RCTs of sufficient quality comparing famciclovir with other oral antiviral therapies for the treatment of genital herpes in HIV-negative people. However, there are RCTs comparing famciclovir with placebo. [17]

Adverse effects from acyclovir or valaciclovir include headache, nausea, malaise, dizziness, arthralgia, rash, agitation, and several less common serious reactions, including hallucinations, encephalopathy, psychosis, seizures, leukopenia, thrombocytopenia, hepatitis and renal toxicity. The study above [16] found nausea and headache to be the most common side effects, and did not report incidence of any other adverse effects. They did state that there were no meaningful laboratory changes between day 1 and 7 for either treatment group.

Clinical guide

It has been established that oral antiviral treatment can decrease symptoms of a first episode of genital herpes in HIV-negative people. [18] [19] [20] In clinical practice, both valaciclovir and aciclovir are considered reasonable first-line options in this situation. Valaciclovir is a prodrug that is converted in vivo to aciclovir, and it has greater oral bio-availability than aciclovir. [21] This allows less frequent dosing with valaciclovir, which may improve patient compliance.

QUESTION What are the effects of different oral antiviral treatments for genital herpes in HIV-positive people?

OPTION DAILY ORAL ANTIVIRAL TREATMENT (ACICLOVIR, VALACICLOVIR, FAMCICLOVIR) FOR PREVENTING RECURRENCE OF GENITAL HERPES IN HIV-POSITIVE PEOPLE

- For GRADE evaluation of interventions for Genital herpes: oral antiviral treatments, see table, p 17 .
- Daily oral antiviral treatment seems to be more effective than placebo in preventing recurrence of genital herpes in HIV-positive people.
- Daily oral valaciclovir does not appear to cause an increase in adverse effects when compared with placebo in HIV-positive women.
- Daily oral valaciclovir and daily oral aciclovir seem equally effective in preventing recurrence of genital herpes in HIV-positive people, but this is based on one RCT.
- We found no RCTs of sufficient quality comparing either oral valaciclovir or oral aciclovir with oral famciclovir in preventing recurrence of genital herpes in HIV-positive people.

Benefits and harms

Daily oral aciclovir versus placebo:

We found three RCTs comparing daily oral aciclovir with placebo. [22] [23] [24]

Recurrence rates

Daily oral aciclovir compared with placebo Daily oral aciclovir may be more effective than placebo at reducing recurrence of genital ulcer disease at up to 24 months in HIV-positive women (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of genital herpes					
[22] RCT	300 women with herpes simplex virus type 2 (HSV-2), HIV positive, and not receiving antiretroviral treatment	**Proportion of women with at least 1 episode of genital ulcer disease , up to 3 months** 11/146 (8%) with aciclovir (400 mg given twice-daily for 3 months) 25/142 (18%) with placebo Of all the women enrolled, 97 had self-reported genital ulcer disease during the 3 months before enrolment (45/151 [30%] in the aciclovir group *v* 52/148 [35%] in the placebo group)	RR 0.43 95% CI 0.22 to 0.84 P = 0.01	●●○	aciclovir
[23] RCT	214 women (Zimbabwean sex workers) with HIV Subgroup analysis	**Recurrent symptomatic genital ulceration , up to 3 months** 0/69 with aciclovir (400 mg given twice-daily for 3 months) 0/56 with placebo 125 HIV-positive women with herpes simplex virus type 2 (HSV-2) included in this analysis	Significance not assessed The RCT was underpowered to detect a clinically important difference between groups as there were fewer than expected HIV-positive women in the study		
[24] RCT	440 people with herpes simplex virus type 2 (HSV-2) and HIV positive	**Prevalence of symptomatic genital ulcer disease , at up to 24 months** with aciclovir (400 mg given twice-daily for 3 months) with placebo Absolute results not reported	Adjusted prevalence rate ratio 0.42 95% CI 0.23 to 0.74 P value not reported See Further information on studies	●●○	aciclovir

Viral shedding

Daily oral aciclovir compared with placebo Daily oral aciclovir may be more effective than placebo at reducing rate of HSV-2 shedding in HIV-positive women (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Viral shedding					
[22] RCT	300 women with herpes simplex virus type 2 (HSV-2), HIV positive, and not receiving antiretroviral treatment	**Proportion of women with detectable genital HSV-2 DNA , 3 months** 10/133 (8%) with aciclovir (400 mg given twice-daily for 3 months) 28/137 (20%) with placebo Of all the women enrolled, 97 had self-reported genital ulcer disease during the 3 months before enrolment (45/151 [30%] in the aci-	RR 0.37 95% CI 0.19 to 0.73 P = 0.002	●●○	aciclovir

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		clovir group *v* 52/148 [35%] in the placebo group)			
[23] RCT	214 women (Zimbabwean sex workers) with HIV Subgroup analysis	**Rates of HSV-2 genital shedding** with aciclovir (400 mg given twice-daily for 3 months) with placebo 125 HIV-positive women with herpes simplex virus type 2 (HSV-2) in this analysis See Further information on studies	OR 0.24 95% CI 0.12 to 0.50 P <0.001 The RCT was underpowered to detect a clinically important difference between groups as there were fewer than expected HIV-positive women in the study	●●○	aciclovir
[24] RCT	440 people with herpes simplex virus type 2 (HSV-2) and HIV positive Subgroup analysis	**Frequency of HSV-2 viral shedding** with aciclovir (400 mg given twice-daily for 24 months) with placebo Absolute results not reported 96 women (43 in the aciclovir group and 53 in the placebo group) who provided at least 12 monthly vaginal swabs (at least 6 months before and 6 months after antiretroviral treatment) included in this analysis See Further information on studies	Adjusted OR 0.13 95% CI 0.04 to 0.41	●●●	aciclovir

Severity of attack

No data from the following reference on this outcome. [22] [23] [24]

Transmission of infection

No data from the following reference on this outcome. [22] [23] [24]

Rate of seroconversion

No data from the following reference on this outcome. [22] [23] [24]

Psychosocial morbidity

No data from the following reference on this outcome. [22] [23] [24]

Quality of life

No data from the following reference on this outcome. [22] [23] [24]

Adverse effects

No data from the following reference on this outcome. [22] [23] [24]

Daily oral valaciclovir versus placebo:

We found three RCTs comparing daily oral valaciclovir with placebo. [25] [26] [27]

Recurrence rates

Daily oral valaciclovir compared with placebo Daily oral valaciclovir seems more effective than placebo at reducing recurrence of genital ulcers and increasing time to recurrence in HIV-positive people (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of genital herpes					
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Freedom from recurrence , 6 months** 65% with valaciclovir 26% with placebo Absolute numbers not reported	RR 2.5 95% CI 1.8 to 3.5	●●○	valaciclovir
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Median time to first recurrence , days** >180 with valaciclovir 59 with placebo	HR 16.7 95% CI 7.3 to 33.3	●●●	valaciclovir
[26] RCT	60 women with HIV receiving antiretroviral treatment and with serological evidence of HSV-2 antibodies	**Proportion of women with at least 1 clinical ulcer episode (defined as 1 episode of genital ulcer or blister in the genital area) , during 3 months of follow-up** 0/30 (0%) with valaciclovir 2/30 (3%) with placebo	P = 0.99	⟷	Not significant
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Recurrence of genital ulceration (defined as at least 1 episode of vesicle or genital ulceration) , at 3 months** 3/68 (5%) with valaciclovir 19/68 (28%) with placebo	RR 0.16 95% CI 0.05 to 0.51 P = 0.002	●●●	valaciclovir

Viral shedding

Daily oral valaciclovir compared with placebo Daily oral valaciclovir may be more effective than placebo at reducing HSV-2 shedding in HIV-positive women. However, the evidence is inconsistent and weak (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Viral shedding					
[26] RCT	60 women with HIV receiving antiretroviral treatment and with serological evidence of HSV-2 antibodies	**Proportion of women recorded as shedding genital HSV-2 DNA at least once , during 3 months of treatment** 9/30 (30%) with valaciclovir (500 mg given twice-daily for 3 months) 13/30 (43%) with placebo	RR 0.66 95% CI 0.33 to 1.31 P = 0.24	⟷	Not significant
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Proportion of women recorded as shedding genital HSV-2 DNA at least once , during 3 months of treatment** 13/68 (19%) with valaciclovir (500 mg given twice-daily for 3 months) 37/68 (54%) with placebo	RR 0.35 95% CI 0.20 to 0.60 P <0.001	●●○	valaciclovir

No data from the following reference on this outcome. [25]

Severity of attack

No data from the following reference on this outcome. [25] [26] [27]

Transmission of infection

No data from the following reference on this outcome. [25] [26] [27]

Rate of seroconversion

No data from the following reference on this outcome. [25] [26] [27]

Psychosocial morbidity

No data from the following reference on this outcome. [25] [26] [27]

Quality of life

No data from the following reference on this outcome. [25] [26] [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Headache** 13% with valaciclovir 8% with placebo Absolute numbers not reported The RCT gave no information on adverse effects in people taking valaciclovir beyond 6 months			
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Fatigue** 8% with valaciclovir 5% with placebo Absolute numbers not reported			
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Influenza** 8% with valaciclovir 3% with placebo Absolute numbers not reported			
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Nasopharyngitis** 8% with valaciclovir 2% with placebo Absolute numbers not reported			
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Rash** 8% with valaciclovir 1% with placebo Absolute numbers not reported			
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Diarrhoea** 12% with valaciclovir 12% with placebo Absolute numbers not reported			
[25] RCT	239 people with HIV and a history of symptomatic recurrent genital herpes	**Nausea** 8% with valaciclovir 8% with placebo Absolute numbers not reported			
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Headache** 20/68 (29%) with valaciclovir 27/68 (40%) with placebo	P = 0.21	⟷	Not significant
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Fatigue** 10/68 (15%) with valaciclovir 17/68 (25%) with placebo	P = 0.13	⟷	Not significant
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and	**Nausea** 11/68 (16%) with valaciclovir 7/68 (10%) with placebo	P = 0.31	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	who had serological evidence of HSV-2 antibodies				
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Vomiting** 4/68 (6%) with valaciclovir 6/68 (9%) with placebo	P = 0.51	⟷	Not significant
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Diarrhoea** 3/68 (4%) with valaciclovir 7/68 (10%) with placebo	P = 0.19	⟷	Not significant
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Constipation** 5/68 (7%) with valaciclovir 10/68 (15%) with placebo	P = 0.17	⟷	Not significant
[27] RCT	140 women with HIV who were ineligible for antiretroviral treatment and who had serological evidence of HSV-2 antibodies	**Hypersensitivity reactions** 10/68 (15%) with valaciclovir 14/68 (21%) with placebo	P = 0.37	⟷	Not significant

No data from the following reference on this outcome. [26]

Daily oral famciclovir versus placebo, daily oral valaciclovir, or daily oral aciclovir:

We found no systematic review or RCTs.

Daily oral valaciclovir versus daily oral aciclovir:

We found one RCT (1062 people with HSV infection and HIV-positive), which compared three treatments (valaciclovir 500 mg twice-daily, valaciclovir 1000 mg once-daily, and aciclovir 400 mg twice-daily) for 48 weeks. [28]

Recurrence rates

Daily oral valaciclovir compared with daily oral aciclovir Daily oral valaciclovir and daily oral aciclovir seem equally effective at reducing time to recurrence of genital ulcers at up to 48 weeks in HIV-positive people (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of genital herpes					
[28] RCT **3-armed trial**	1062 people with HSV and HIV-positive	**Time to recurrence of genital ulcers , up to 48 weeks** with lower-dose valaciclovir with aciclovir	HR 0.73 95% CI 0.50 to 1.06 P = 0.10	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported Remaining arm evaluated higher-dose valaciclovir			
[28] RCT **3-armed trial**	1062 people with HSV and HIV positive	**Time to recurrence of genital ulcers , up to 48 weeks** with higher-dose valaciclovir with aciclovir Absolute results not reported Remaining arm evaluated lower-dose valaciclovir	HR 1.31 95% CI 0.94 to 1.82 P = 0.11	⟷	Not significant

Viral shedding

No data from the following reference on this outcome. [28]

Severity of attack

No data from the following reference on this outcome. [28]

Transmission of infection

No data from the following reference on this outcome. [28]

Rate of seroconversion

No data from the following reference on this outcome. [28]

Psychosocial morbidity

No data from the following reference on this outcome. [28]

Quality of life

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT **3-armed trial**	1062 people	**Adverse effects leading to withdrawal, including nausea and headache** 11% with valaciclovir (higher or lower dose) 9% with aciclovir Absolute numbers not reported	Significance not assessed		

Further information on studies

[23] The RCT reported that a larger proportion of women were shedding HSV-2 at baseline in the aciclovir group (20/69 [29%]) *v* placebo group (9/56 [16%]), but the difference was reported as not significant (P value not reported). HSV-2 shedding during the study was 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 *v* 123/531 (23%) with placebo.

[24] The RCT was in people aged at least 18 years from Rakai, Uganda, who were HIV positive (CD4 count 300–400 cells/microlitre) and co-infected with HSV-2. Prevalence risk ratios were adjusted to account for multiple observations in the same individual. HSV-2 viral shedding was detected in 81/792 (10%) of visits in the placebo group *v* 4/288 (1%) in the aciclovir group; unadjusted OR 0.10 (95% CI 0.03 to 0.31).

Comment:

Valaciclovir significantly reduced the rate of recurrences of genital herpes. However, 35% of people being treated had a recurrence within 6 months. [25] 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). [28]

In the past, there was some controversy regarding the biological and clinical meaning of asymptomatic HSV-2 infection. [29] However, one study 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. [29] 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 more than 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. [12]

OPTION ORAL ANTIVIRAL TREATMENTS (ACICLOVIR, FAMCICLOVIR, VALACICLOVIR) VERSUS EACH OTHER FOR A FIRST EPISODE OF GENITAL HERPES IN HIV-POSITIVE PEOPLE

- For GRADE evaluation of interventions for Genital herpes: oral antiviral treatments, see table, p 17 .
- We found no RCTs of sufficient quality to assess whether one oral antiviral treatment (aciclovir, valaciclovir, or famciclovir) is more effective than another for treating a first episode of genital herpes in HIV-positive people.

Benefits and harms

Oral antiviral treatments (aciclovir, valaciclovir, famciclovir) versus each other:

We found no systematic review or RCTs examining effects of oral antiviral treatments versus each other for first episodes of genital herpes in HIV-positive people.

Comment: **Clinical guide**
Current consensus is that oral antiviral treatment is effective for the treatment of first-episode genital herpes in people with HIV. However, we are unable to comment on whether one oral antiviral treatment (aciclovir, valaciclovir, or famciclovir) is more effective than another as we found insufficient evidence.

GLOSSARY

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

Daily oral antiviral treatment (aciclovir, valaciclovir, famciclovir) for preventing recurrence of genital herpes in HIV-positive people One RCT added. [24] Categorisation unchanged (beneficial).

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Genital herpes: oral antiviral treatments

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Disclaimer

GRADE **Evaluation of interventions for Genital herpes: oral antiviral treatments.**

Important outcomes	Psychosocial morbidity, Quality of life, Rate of seroconversion, Recurrence rates, Severity of attack, Transmission of infection, Viral shedding								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of different oral antiviral treatments versus each other for a first episode of genital herpes in HIV-negative people?									
1 (643) [16]	Severity of attack	Oral valaciclovir versus oral aciclovir	4	0	0	0	0	High	
1 (643) [16]	Viral shedding	Oral valaciclovir versus oral aciclovir	4	0	0	0	0	High	
What are the effects of different oral antiviral treatments for genital herpes in HIV-positive people?									
3 (865) [22] [23] [24]	Recurrence rates	Daily oral aciclovir versus placebo	4	–3	0	0	0	Very low	Quality points deducted for subgroup analysis in 1 RCT, for 1 RCT being under-powered to detect a clinically important difference between groups, and for incomplete reporting of results in 1 RCT
3 (521) [22] [23] [24]	Viral shedding	Daily oral aciclovir versus placebo	4	–3	0	0	+1	Low	Quality points deducted for subgroup analysis in 1 RCT, for 1 RCT being underpowered to detect a clinically important difference between groups, and for incomplete reporting of results in 1 RCT; effect size point added for RR <0.5
3 (435) [25] [26] [27]	Recurrence rates	Daily oral valaciclovir versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results in largest RCT
2 (196) [26] [27]	Viral shedding	Daily oral valaciclovir versus placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data, and consistency point deducted for conflicting results between studies
1 (1062) [28]	Recurrence rates	Daily oral valaciclovir versus daily oral aciclovir	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.