World Health Organization

WHO GUIDELINES FOR THE

Treatment of *Genital Herpes Simplex Virus*

Web annex D: Evidence tables and evidence-to-decision frameworks

September 2016

The full guidelines are available at:
www.who.int/reproductivehealth/publications/rtis/genital-HSV-treatment-guidelines/en/

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CONTENTS

RECOMMENDATION 1

Should treatment versus no treatment be provided for first clinical episodes of herpes simplex virus?	
Population:	First clinical episodes of herpes simplex virus
Intervention:	Treatment
Comparison:	No treatment
Main outcomes:	**Critical:** Duration of clinical episode, HSV-2 severity/pain, quality of life **Important:** Ulcer healing, side-effects, HSV-2 transmission, duration of shedding, compliance
Setting:	Outpatient
Perspective:	Population
Background:	The herpes simplex virus (HSV), or herpes, is categorized into two types: herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). Both HSV-1 and HSV-2 are highly infectious. HSV-1 is transmitted by oral-to-oral contact and mainly causes herpes labialis, or "cold sores", but can also cause genital herpes. HSV-2 is a sexually transmitted infection (STI) that can cause genital herpes. Most infections are transmitted via asymptomatic viral shedding. Oral antiviral medications are available for initial, episodic, and suppressive therapy; however, there is no cure for the infection. The medications can vary: aciclovir, famciclovir and valaciclovir. In 2003, World Health Organization (WHO) guidelines recommended dosages are: aciclovir, 200 mg orally, 5 times daily for 7 days; aciclovir, 400 mg orally, 3 times daily for 7 days; valaciclovir, 1 g orally, twice daily for 7 days; or famciclovir, 250 mg orally, 3 times daily for 7 days. The Guideline Development Group (GDG) identified the above treatments for review.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Globally in 2012, it was estimated that over 417 million people were currently infected with HSV-2. For new infections, in people 15–49 years old (2012), it was estimated at 19.2 million, of whom 11.8 million were women and 7.4 million were men. Estimates are heterogeneous across regions, but typically greater in low- and middle-income countries (with the exception of the USA). When symptoms of genital herpes occur, there are generally one or more genital or anal blisters called ulcers. First-episode infections of genital herpes are more extensive, and primary lesions last two to six weeks versus approximately one week for lesions in recurrent disease. First clinical episodes can also be associated with central nervous system, fever and flu-like symptoms. Social stigma and other social sequelae can occur. Infection with HSV-2 also may increase the risk of acquiring HIV infection. Moreover, HSV-2 can be transmitted to neonates from an infected pregnant mother.
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • **Moderate** • Large • Varies • Don't know	**Research evidence:** We found a Cochrane protocol by Heslop (2013), and data was provided from this review. We included 5 randomized controlled trials (RCTs) comparing aciclovir in different doses compared to placebo: Nilsen (1982), Bryson (1983), Corey (1983), Mertz (1984) and Kinghorn (1986). In addition, data from 3 RCTs pooled in Weiss (2011) were used. We did not find studies that evaluated valaciclovir or famciclovir compared to no treatment/placebo. Data for other subgroups were not available (e.g. people with positive HIV status, people who are immunocompromised and pregnant women). A summary of the findings from these studies is provided in the Evidence Table. **Additional considerations:** Various oral dosages of aciclovir were used and were provided for 5–10 days; 1 study assessed intravenous administration. Differences in duration of symptoms and lesions is probably reduced with aciclovir and ranged from 2–4 days. Pain may be reduced by 2 days (mean difference [MD]: 2.1 days fewer; 95% CI: 2.95–1.25). The duration of viral shedding may be reduced by 9 days (MD: 9.2 days fewer; 95% CI: 11.1–7.29). The GDG agreed that the effects of treatment would likely be similar in other populations (e.g. people with positive HIV status, people who are immunocompromised and pregnant women). This data were used to also inform recommendations for people with "severe infections". Severe infections have traditionally not been well defined, although first clinical episodes can often be severe. Therefore, the benefits would likely apply to people with "severe infections".
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • Low • **Moderate** • High • No included studies	**Additional considerations:** Most studies did not report on randomization methods or allocation concealment. However, the GDG agreed that the omission is likely due to reporting issues in journals and likely performed in the studies. Imprecision was a factor for some outcomes due to few events but was considered with risk of bias of the studies and the evidence downgraded to moderate. The GDG agreed that it was unlikely that any negative studies were not captured. The group conceded that it was unlikely that new trials would be done, given that it might be unethical to not provide treatment.

<table>
<tr><td>Values</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?

• Important uncertainty or variability
• Possibly important uncertainty or variability
• Probably no important uncertainty or variability
• No important uncertainty or variability</td><td>Research evidence:
A discrete choice exercise suggested subjects' preferences were influenced by both the treatment they follow and attributes of treatment including cost. Of all the attributes, patients place high value in unit change in chance of recurrence (1%), followed by unit change in number of tablets taken daily (1 tablet), unit change in chance of becoming infected with HIV, unit change in number of tablets taken in addition during each recurrence.

In addition, qualitative studies also suggested stigma related is also an attribute.</td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?

• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention
• Varies
• Don't know</td><td></td></tr>
<tr><td>Resources required</td><td>How large are the resource requirements (costs)?

• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings
• Varies
• Don't know</td><td>
<table>
<tr><th>A</th><th>B</th><th>C</th><th>D*</th><th>E</th><th>F</th></tr>
<tr><td>Aciclovir 200 mg po</td><td>5</td><td>5–10 days</td><td>$0.05</td><td>$1.25 to $2.50</td><td>$1.56 to $3.12</td></tr>
<tr><td>Aciclovir 400 mg po</td><td>3</td><td>5–10 days</td><td>$0.04</td><td>$0.60 to $1.20</td><td>$0.75 to $1.50</td></tr>
<tr><td>Valaciclovir 500 mg – 1 g po</td><td>2</td><td>5–10 days</td><td>$0.625</td><td>$6.25 to $12.50</td><td>$7.81 to $15.60</td></tr>
<tr><td>Famciclovir 250 mg po</td><td>3</td><td>5–10 days</td><td>$4.38</td><td>$13.14 to $26.28</td><td>$16.42 to $32.85</td></tr>
</table>
*Sources: International drug price indicator guide (MSH, 2015) and www.drugs.com
A: treatment; B: doses per day; C: treatment duration; D: drug cost per dose; E: drug cost per full-course treatment; F: 25% procurement as defined by International drug price indicator guide (MSH, 2015).
po: orally

Additional considerations:
The GDG wondered why the higher dose was less expensive than the smaller one and assumed this was due to economies of scale. The group concluded that across several settings, the cost was probably considered moderate, although valaciclovir was more expensive than aciclovir, and famciclovir was known to be the most expensive.</td></tr>
<tr><td>Certainty of evidence of required resources</td><td>What is the certainty of the evidence of resource requirements (costs)?

• Very low
• Low
• Moderate
• High
• No included studies</td><td>Research evidence:
Data for cost not based on research studies.

Additional considerations:
None</td></tr>
</table>

Cost effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • **Favours the intervention** • Varies • No included studies	**Research evidence:** No research evidence available. **Additional considerations:** The GDG agreed that there were moderate costs for moderate benefits. Therefore, the treatment is favoured over the placebo.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • **Varies** • Don't know	**Research evidence:** No research evidence available. **Additional considerations:** Out of pocket expenses may affect people differently in countries. If covered, then it would not lead to out-of-pocket payments and not lead to inequity. The GDG agreed that equity effects were unclear. If the drugs are too expensive, equity would only increase for those who can pay for it in out-of-pocket payments. However, a recommendation could lead to better coverage.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • Yes • **Varies** • Don't know	**Research evidence:** We searched for reviews and studies specific to herpes treatment acceptability. A systematic review of the literature for treatment utilization in sexually transmitted diseases (in India) reported that utilization ranged from 16% to 55% in the community-based studies and was higher (~70%) in research trials. Treatment may not be acceptable to patients due to the resources and availability of services, social factors and distance. Non-utilization was also due to ignorance, illiteracy and lack of awareness; and women reported a lack of female doctors, being afraid of results and judgement of doctors, stigma, shyness and embarrassment. Cost of care and less faith in clinical care were also factors. Compliance data from some RCTs (see Evidence tables) indicated little or no difference in compliance between different regimens. An overview of reviews of medication adherence (Ryan, 2014) reported that adherence may be improved with simpler drug regimens. However, when compliance was measured in the studies included for HSV treatments, compliance was similar between drugs. **Additional considerations:** The GDG agreed that if personal payment was required for drugs, it may not be acceptable. The GDG did not believe that the drugs would be unacceptable to key stakeholders, other than by availability and cost.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes**	**Research evidence:** No research evidence available. **Additional considerations:** The treatment was considered widely available, but cost was still a concern. Additionally, there was concern that the drug might not be paid for by health systems or donors as the infection was considered recurrent, ignoring the more detrimental effects of the first infection.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Should treatment versus no treatment be provided for first clinical episodes of herpes simplex virus type 2?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention •	Strong recommendation for the intervention ●
Recommendation	For adults and adolescents with a first clinical episode of genital HSV infection, the WHO STI guideline recommends treatment over no treatment. *Strong recommendation, moderate quality evidence* **Remarks:** This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.				
Justification	The evidence for treatment of a first clinical episode of genital HSV infection compared to no treatment was of moderate quality. Data from eight randomized controlled trials were reported in six articles comparing aciclovir to no treatment or placebo. In these trials, various oral dosages of aciclovir were used over periods of 5–10 days. One study assessed intravenous administration. The findings indicate that the duration of symptoms and lesions is probably reduced (2–4 days fewer) with aciclovir compared to placebo. Pain may be reduced by two more days (mean difference [MD]: 2.1 days fewer; 95% confidence interval (CI): 2.95–1.25). The duration of viral shedding may be reduced by nine more days (MD: 9.2 days fewer; 95% CI: 11.1–7.29). Adverse events may also be reduced with treatment compared to placebo. No studies were found comparing valaciclovir or famciclovir to no treatment. The GDG agreed that the magnitude of the benefits of treatment was moderate and the adverse events trivial. The GDG agreed that there would be little variability in patient values and preferences relating to the different medicines and treatment regimens. However, higher value is likely to be placed on reducing the number and frequency of tablets taken. Research relating to other conditions indicates that adherence to treatment regimens may be improved with simpler regimens, although when compliance was measured in the studies included for HSV treatments, compliance was similar between medicines and regimens. Overall, it was agreed that the different regimens and medicines are probably acceptable to most people. Both valaciclovir and famciclovir are more expensive than aciclovir, and famciclovir is more expensive than valaciclovir. Where the medicines are a direct cost to people with HSV, the more expensive medicines would probably reduce equity if recommended.				
Subgroup considerations	This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.				
Implementation considerations					
Monitoring and evaluation					
Research priorities	Little evidence was found for outcomes critical to making decisions about drugs to treat first or recurrent episodes of genital HSV infections. Important patient outcomes should be measured in clinical trials, such as genital HSV acquisition and transmission, HIV acquisition and transmission, quality of life and pain. There were few available data for direct comparisons of different drugs, in particular, for comparisons with famciclovir. There were also few studies comparing the different dosages of the drugs. Future research could use the dosages recommended in these guidelines as comparators. Equity issues, acceptance of and compliance with different drugs and regimens should also be explored in people with genital HSV infections. Although this search was not limited to different populations, there were few data for key populations, such as people with HIV infection, people who were immunocompromised and pregnant women. More information can also be provided to allow for the critical appraisal of clinical trials by following the standards of reporting of RCTs, in particular for the methods of randomization and allocation concealment and blinding.				

EVIDENCE TABLE

Aciclovir versus placebo

Bryson 1983	Aciclovir: 200 mg capsule po) 5 × a day × 10 days Placebo: placebo capsule po 5 × a day × 10 days
Kinghorn 1986	Aciclovir: 200 mg tablets po 5 × a day × 7 days Placebo: placebo tablets po 5 × a day × 7 days
Nilsen 1982	Aciclovir: 2 × 100 mg capsules po 5 × a day × 5 days Placebo: 2 placebo capsules po 5 × a day × 5 days
Mertz 1984	Aciclovir: 200 mg capsule po 5 × a day × 10 days Placebo: placebo capsule po 5 × a day × 10 days
Corey 1983	Aciclovir intravenous (IV): 5 mg/kg IV over 1 hour × 5 days (15 doses) every 8 hours Placebo: normal saline IV over 1 hour 5 days (15 doses), every 8 hours
Weiss 2011 (Maynaud 2009, Phiri 2010, Paz-Bailey 2009)	Aciclovir 400 mg 3 × a day × 5 days OR aciclovir 800 mg 2 × a day × 5 days Placebo 3 × a day × 5 days OR placebo 2 × a day × 5 days

IV: intravenous; po: orally

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aciclovir	Placebo	Relative (95% CI)	Absolute (95% CI)		
Duration of symptoms from onset of treatment (assessed with: time to resolution)												
5	Randomized trials	Not serious[1]	Not serious	Not serious	Serious[1]	None	119	119	_	MD **3.2 days fewer** (4.94–1.46 fewer)[2]	⨁⨁⨁◯ MODERATE	CRITICAL
Pain												
3	Randomized trials	Serious[3]	Not serious	Not serious	Serious[3]	None	69	60	_	MD **2.1 days fewer** (2.95–1.25 fewer)[4]	⨁⨁◯◯ LOW	CRITICAL
Quality of life – not measured												**CRITICAL**
Duration of lesions from onset of treatment												
5	Randomized trials	Not serious[1]	Not serious	Not serious	Serious[1]	None	197	193	_	MD **3.51 days fewer** (6.19–0.82 fewer)[1]	⨁⨁⨁◯ MODERATE	IMPORTANT
Duration of viral shedding												
3	Randomized trials	Serious[3]	Not serious	Not serious	Serious[3]	None	69	60	_	MD **9.2 days fewer** (11.1–7.29 fewer)[5]	⨁⨁◯◯ LOW	IMPORTANT
Adverse Events – any adverse event												
2	Randomized trials	Serious[3]	Not serious	Not serious	Serious[3]	None	11/130 (8.5%)	15/133 (11.3%)	**RR 0.74** (0.36–1.53)	**29 fewer per 1000** (from 60 more to 72 fewer)	⨁⨁◯◯ LOW	IMPORTANT
HSV-2 transmission – not measured												

CI: confidence interval; MD: mean difference

1. Randomization and blinding process were unclear in most studies but not downgraded and instead considered with imprecision due to few participants.
2. Two of the five studies were used in the meta-analysis, with similar results in the other three. Weiss (2011) also reported slightly faster healing with aciclovir ($P = 0.04$) but in people with HSV-2 or other ulcers.
3. Randomization and blinding process were unclear, and there was imprecision due to few participants.
4. Kinghorn (1986) reported MD. Two other studies (Corey 1983 and Nilsen 1982) reported median values that were consistent.
5. MD from one study and the two other studies showed consistent results. The 95% CI did not exclude no difference between the interventions.

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Patient values and preferences, acceptability and cost: specific to herpes simplex virus infections

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Patient values and preferences, acceptability and cost: other sexually transmitted infections and conditions

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RECOMMENDATION 2

Should aciclovir, valaciclovir or famciclovir be used for the treatment of first clinical episodes of herpes simplex virus type 2 infections?	
Population:	First clinical episodes of HSV-2
Intervention or Comparison:	Aciclovir, Valaciclovir, Famciclovir
Main outcomes:	**Critical:** Duration of clinical episode, HSV-2 severity/pain, quality of life **Important:** Ulcer healing, side-effects, HSV-2 transmission, duration of shedding, compliance For pregnant women critical outcomes: Maternal outcomes (caesarean section), fetal outcomes (neonatal herpes – meningo-encephalitis, fever, hepatitis), teratogenicity, fetal loss, toxicity, neonatal death)
Setting:	Outpatient
Perspective:	Population
Background:	The herpes simplex virus (HSV), or herpes, is categorized into two types: herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2). Both HSV-1 and HSV-2 are highly infectious. HSV-1 is transmitted by oral-to-oral contact and mainly causes herpes labialis, or "cold sores", but can also cause genital herpes. HSV-2 is a sexually transmitted infection that can cause genital herpes. Most infections are transmitted via asymptomatic viral shedding. Oral antiviral medications are available for initial, episodic and suppressive therapy; however, there is no cure for the infection. The medications can vary: aciclovir, famciclovir and valaciclovir. In 2003, WHO guidelines recommended aciclovir, 200 mg orally, 5 times daily for 7 days; aciclovir, 400 mg orally, 3 times daily for 7 days; valaciclovir, 1 g orally, twice daily for 7 days; or famciclovir, 250 mg orally, 3 times daily for 7 days. The Guideline Development Group (GDG) identified these treatments for review.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Globally, in 2012, it was estimated that over 417 million people were currently infected with HSV-2. For new infections in people 15–49 years old (2012), it was estimated at 19.2 million, of whom 11.8 million were women and 7.4 million were men. Estimates are heterogeneous across regions, but typically greater in low and middle–income countries (with the exception of US). When symptoms of genital herpes occur, there are generally one or more genital or anal blisters called ulcers. First-episode genital herpes infections are more extensive, and primary lesions last two to six weeks versus approximately one week for lesions in recurrent disease. First clinical episodes can also be associated with central nervous system, fever and flu-like symptoms. Social stigma and other social sequelae can occur. Infection with HSV-2 also may increase the risk of acquiring HIV infection. Moreover, HSV-2 can be transmitted to neonates from an infected pregnant mother.
Desirable Effects	**How substantial are the desirable anticipated effects?** • **Trivial** • Small • Moderate • Large • Varies • Don't know	**Research evidence:** We found a Cochrane protocol by Heslop (2013), and data was provided from this review. We included 3 RCTs comparing valaciclovir to aciclovir, famciclovir to aciclovir, and aciclovir at different doses. We also added Loveless (1997) from our search, which was an analysis of three RCTs comparing famciclovir to aciclovir. Data for other subgroups was not available (e.g. people with positive HIV status, people who are immunocompromised, and pregnant women). A summary of the findings from these studies is provided in the evidence tables. **Additional considerations:** No data was available for certain dosages. Different dosages of aciclovir, valaciclovir and famciclovir were compared with each other. Two trials compared aciclovir and valaciclovir and found that there were probably little-to-no differences for duration of viral shedding, lesions, symptoms and adverse events (moderate quality evidence). One trial compared aciclovir to famciclovir and found that there may be little-to-no differences for outcomes (low quality evidence). Another trial compared famciclovir to valaciclovir and found that there were probably little-to-no differences for outcomes (moderate quality evidence). The GDG agreed that there are trivial differences in benefits and harms between treatments. Different dosages of aciclovir were compared in two trials (200 mg 5 times daily for 5 days versus alternatives). There may be little-to-no difference between the doses for outcomes. Different dosages of valaciclovir were compared in 4 trials (500 mg twice daily for 5 days versus alternatives). There are probably little-to-no differences between the doses for outcomes. Famciclovir at 125, 250 or 500 mg twice daily for 5 days were compared, and there may be little-to-no differences in outcomes across the different dosages. For all drugs, quality of life and HSV or HIV transmission were not measured. Viral shedding was measured in some studies, but the GDG agreed that this measure was not a useful surrogate for HSV transmission.
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • Low • **Moderate** • High • No included studies	**Additional considerations:** The quality of the evidence was moderate for some comparisons, but low quality for other comparisons and very low quality for comparisons (e.g. high- and low-dose aciclovir). Most studies did not report on randomization methods or allocation concealment. However, the GDG agreed that the omission is likely due to reporting issues in journals and likely performed in the studies. Imprecision was a factor for some outcomes due to few events but was considered with risk of bias of the studies and the evidence downgraded to moderate. The GDG agreed that it is unlikely that negative studies were not captured.

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<td>Values</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?

• Important uncertainty or variability
• Possibly important uncertainty or variability
• Probably no important uncertainty or variability
• No important uncertainty or variability
• No known undesirable outcomes</td>
<td>Research evidence:
A discrete choice exercise suggested subjects' preferences were influenced by both the treatment they follow and attributes of treatment including cost. Of all the attributes, patients place high value in unit change in chance of recurrence (1%), followed by unit change in number of tablets taken daily (1 tablet), unit change in chance of becoming infected with HIV, unit change in number of tablets taken in addition during each recurrence.

Qualitative studies also suggested stigma related was important.</td>
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<tr>
<td>Balance of effects</td>
<td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?

• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention
• Varies
• Don't know</td>
<td>Research evidence:
No research evidence was identified.

Additional considerations:
The GDG agreed that the differences between drugs were trivial for benefits and harms and therefore did not favour one over another. Other factors such as cost, feasibility, acceptability, may decide use.</td>
</tr>
<tr>
<td>Resources required</td>
<td>How large are the resource requirements (costs)?

• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings
• Varies
• Don't know</td>
<td>Research evidence:

<table>
<tr><th>A</th><th>B</th><th>C</th><th>D*</th><th>E</th><th>F</th></tr>
<tr><td>aciclovir 200 mg po</td><td>5</td><td>5–10 days</td><td>$0.05</td><td>$1.25 to $2.50</td><td>$1.56 to $3.12</td></tr>
<tr><td>aciclovir 400 mg po</td><td>3</td><td>5–10 days</td><td>$0.04</td><td>$0.60 to $1.20</td><td>$0.75 to $1.50</td></tr>
<tr><td>valaciclovir 500 mg – 1 g po</td><td>2</td><td>5–10 days</td><td>$0.625</td><td>$6.25 to $12.50</td><td>$7.81 to $15.60</td></tr>
<tr><td>famciclovir 250 mg po</td><td>3</td><td>5–10 days</td><td>$4.38</td><td>$13.14 to $26.28</td><td>$16.42 to $32.80</td></tr>
</table>

*Sources: International drug price indicator guide (MSH, 2015) and www.drugs.com
A: treatment; B: dose per day; C: treatment duration; D: drug cost, per dose; E: drug cost per full-course treatment; F: 25% procurement as defined by International drug price indicator guide (MSH, 2015)
po: orally

Additional considerations:
The GDG wondered why the higher dose was less expensive than the smaller one and assumed this was due to economies of scale. The group concluded that across several settings, the cost was probably considered moderate, although valaciclovir was more expensive than aciclovir, and famciclovir was known to be the most expensive. Valaciclovir is approximately 10 times more expensive than aciclovir.</td>
</tr>
</table>

Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** • Very low • Low • Moderate • High • **No included studies**	**Research evidence:** No research evidence available.
Cost effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • **Varies** • No included studies	**Research evidence:** No research evidence available. **Additional considerations:** The GDG agreed that there were moderate costs for moderate benefits. However, cost effectiveness would vary with aciclovir versus famciclovir or valaciclovir.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • **Varies** • Don't know	**Research evidence:** No research evidence was identified. **Additional considerations:** Out of pocket expenses may affect people differently in countries. If coverage, then would not lead to out of pocket payments and not lead to inequity. The GDG agreed that equity effects were unclear. If the drugs were too expensive, equity would only increase for those who can pay for it in out of pocket payments. However, a recommendation could lead to better coverage. Overall, the GDG was concerned that higher costs of valaciclovir and famciclovir could contribute to decreasing equity if recommended.

Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • Yes • **Varies** • Don't know	**Research evidence:** We searched for reviews and studies specific to herpes treatment acceptability. A systematic review of the literature for use of treatments in sexually transmitted diseases (in India) reported that utilization ranged from 16% to 55% in the community-based studies and was higher (~70%) in research trials. Treatment might not be acceptable to patients due to the resources and availability of services, social factors, and distance. Non-utilization was also due to ignorance, illiteracy and lack of awareness; and women reported a lack of female doctors, being afraid of results and judgement of doctors, stigma, shyness, and embarrassment. Cost of care and less faith in clinical care were also factors. An overview of reviews of medication adherence (Ryan, 2014) reported that adherence might be improved with simpler drug regimens. However, when compliance was measured in the studies included for HSV treatments, compliance was similar between drugs. **Additional considerations:** The GDG suggested that the easier regimen of valaciclovir could be beneficial in settings that could afford it and where compliance was an issue. However, there was little-to-no difference in compliance when measured in trials, and compliance is likely dependent on the presence of symptoms. The GDG agreed that if personal payment was required for drugs, it might not be acceptable. The GDG did not believe that the drugs would be unacceptable to key stakeholders, other than by availability and cost.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** No research evidence was identified. **Additional considerations:** The treatment was considered widely available, but cost was still a concern. Additionally, there was concern that the drug might not be paid for by health systems or donors as the infection was considered recurrent, ignoring the more detrimental effects of the first infection. The GDG agreed that follow-up during the course of treatment might not be possible in some settings, and symptoms of the first clinical episode might be prolonged. For these reasons, the GDG agreed that therapy for a longer duration should be provided (e.g. for 10 days).

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Should aciclovir, valaciclovir or famciclovir be used for the treatment of first clinical episodes of herpes simplex virus type 2 infections?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Recommendation	For adults and adolescents with a first clinical episode of genital HSV infection, the WHO STI guideline suggests a standard dose of aciclovir over valaciclovir or famciclovir. *Conditional recommendation, moderate quality evidence* Dosages: • aciclovir 400 mg orally thrice daily for 10 days (standard dose) • aciclovir 200 mg orally 5 times daily for 10 days • valaciclovir 500 mg orally twice daily for 10 days • famciclovir 250 mg orally thrice daily for 10 days **Remarks**: Given that follow-up visits may not be possible during the course of treatment and symptoms of the first clinical episode may be prolonged, therapy is provided for 10 days. Although the benefits of the medicines are probably similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of medicine may also depend on compliance considerations. This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.				
Justification	The overall quality of the evidence for the comparisons between aciclovir, valaciclovir and famciclovir was moderate to low. Two studies compared aciclovir (200 mg five times daily for 7 or 10 days) to valaciclovir (300 mg or 1000 mg twice daily for 7 or 10 days). The findings indicate that the duration of symptoms, viral shedding and pain, and levels of compliance and risk of adverse events are probably similar with either medicine. Different dosages of famciclovir (125, 250, 500 or 750 mg thrice daily for 5 or 10 days) were compared to aciclovir (200 mg five times daily for 5 or 10 days) in three studies. Findings indicate that the duration of lesions, symptoms and viral shedding and risk of adverse events are probably similar with either medicine, and probably similar between 5- or 10-day treatment duration with 250 mg and 500 mg famciclovir. One other small study compared a standard dose of aciclovir at 1000 mg daily to 4000 mg daily for 10 days. Although the evidence is uncertain (i.e. very low quality for this comparison), the findings indicate that the higher daily dose (4000 mg) may reduce the duration of pain by two days, but may increase the duration of lesions by one day and may increase the risk of adverse events; the duration of viral shedding was shown to be similar with either dose. Overall, the GDG agreed that there were trivial differences between medicines in terms of the benefits or adverse events, and trivial increases in the benefits gained from higher doses of aciclovir. The GDG also agreed that pharmacokinetic data for the different medicine regimens supported those using fewer tablets and shorter treatment durations (e.g. for 5 days). However, follow-up visits may not be possible during the course of treatment in some settings and symptoms of the first clinical episode may be prolonged, in addition to the fact that neurologic complications, such as meningitis and urinary retention, tend to occur towards the end of the episode. Therefore, although these complications are rare, the GDG agreed that therapy should be provided for a longer duration than 5 days, given the safety of the medicine, the potential benefits of the medicine and lack of concern about resistance. As there is a high probability of patients not returning for follow-up, and to facilitate procurement, packaging and dispensing, the GDG recommended a 10-day regimen rather than a range (for 7–10 days). For all medicines in the studies reviewed, quality of life and transmission of HSV or HIV were not measured. Viral shedding was measured in some studies, but the GDG agreed that this measure was not a useful surrogate for HSV transmission.				

CONCLUSIONS

Should aciclovir, valaciclovir or famciclovir be used for the treatment of first clinical episodes of herpes simplex virus type 2 infections?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Justification	The GDG agreed that there would be little variability in patient values and preferences relating to the different medicines and treatment regimens. However, higher value is likely to be placed on reducing the number and frequency of tablets taken. Research relating to other conditions indicates that adherence to treatment regimens may be improved with simpler regimens, although when compliance was measured in the studies included for HSV treatments, compliance was similar between medicines and regimens. Overall, it was agreed that the different regimens and medicines are probably acceptable to most people. Both valaciclovir and famciclovir are more expensive than aciclovir, and famciclovir is more expensive than valaciclovir. Where the medicines are a direct cost to people with HSV, the more expensive medicines would probably reduce equity if recommended. In summary, there are probably moderate benefits of treatment over no treatment, and trivial differences between medicines in terms of the benefits and adverse events. There is probably no important uncertainty or variability in patients values and preferences relating to the different medicines and treatment regimens, but acceptability may vary depending on the medicine dosages. All medicines are feasible to provide, but aciclovir costs less than famciclovir or valaciclovir.				
Subgroup considerations	This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.				
Implementation considerations					
Monitoring and evaluation					
Research priorities	Little evidence was found for outcomes critical to making decisions about drugs to treat first or recurrent episodes of genital HSV infections. Important patient outcomes should be measured in clinical trials, such as genital HSV acquisition and transmission, HIV acquisition and transmission, quality of life and pain. There were few available data for direct comparisons of different drugs, in particular for comparisons with famciclovir. There were also few studies comparing the different dosages of the drugs. Future research could use the dosages recommended in these guidelines as comparators. Equity issues, acceptance of and compliance with different drugs and regimens should also be explored in people with genital HSV infections. Although this search was not limited to different populations, there were few data for key populations, such as people with HIV infection, people who are immunocompromised and pregnant women. More information can also be provided to allow for the critical appraisal of clinical trials by following the standards of reporting of RCTs, in particular for the methods of randomization and allocation concealment and blinding.				

EVIDENCE TABLES

Aciclovir versus valaciclovir

Fife 1997	valaciclovir 1000 mg 2 × a day × 10 days aciclovir 200 mg 5 × a day × 10 days	**Lai 2000**	aciclovir 200 mg 5 × a day × 7–10 days valaciclovir 300 mg 2 × a day × 7–10 days

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Valaciclovir	Aciclovir	Relative (95% CI)	Absolute (95% CI)		
Duration of symptoms from onset of treatment												
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious[1]	None	336	335	–	MD **0.3 days more** (0.81 fewer to 1.41 more)[2]	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life – not measured												
Pain												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious[1]	None	323	320	–	Median **5 days in each group**[3]	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of viral shedding												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious[1]	None	323	320	–	Median **3 days in each group**[4]	⨁⨁⨁◯ MODERATE	IMPORTANT
HSV-2 transmission – not measured												
Adverse events – any adverse event												
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious[1]	None	61/336 (18.2%)	54/335 (16.1%)	**RR 1.12** (0.81–1.57)	19 more per 1000 (from 31 fewer to 92 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Compliance												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious[1]	None	The patients were generally compliant: only 46 patients (25 receiving valaciclovir and 21 receiving aciclovir) failed to take at least 80% of their study medication.				⨁⨁⨁◯ MODERATE	IMPORTANT

MD: mean difference; HR: hazard ratio; RR: relative risk

1. Unclear randomization, blinding and loss to follow-up in some trials but considered with some imprecision around the effect.
2. MD reported from one study, and the larger study (n = 643) reported HR 1.02 (0.85–1.22).
3. HR 1.0 (0.85–1.18) also reported
4. HR also reported 1.01 (0.85–1.20).

FAMCICLOVIR VERSUS ACICLOVIR

Loveless 1997 (data from 3 RCTs)	famciclovir tid 250 mg, 500 mg or 750 mg × 5 days aciclovir 200 mg 5 × daily × 5 days	famciclovir tid 125 mg, 250 mg or 500 mg × 10 days aciclovir 200 mg 5 × daily × 10 days

Quality assessment							No. of patients		Effect	Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Famciclovir	Aciclovir			
Duration of lesions from onset of treatment (assessed with: median time to complete healing)											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	712	238	Median 7–8 days with famciclovir and 6–7 days with aciclovir (similar)	⨁⨁⨁◯ MODERATE	IMPORTANT
Pain – not measured											
Quality of life – not measured											
Adverse events – Drug toxicity (assessed with: number of events)											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	712	238	Mild nausea and dizziness reported events with famciclovir	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of symptoms from onset of treatment											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	375	123	Median 6–8 days for 5-day famciclovir, 8–12 days for 10-day famciclovir and 7–13 days with aciclovir (similar)	⨁⨁⨁◯ MODERATE	IMPORTANT
HSV-2 transmission – not measured											
Compliance – not measured											
Duration of viral shedding (median time to cessation viral shedding)											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	555	190	Median 2–3 days with famciclovir and 3 days with aciclovir (similar)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: confidence intervals; MD: mean difference; RR: relative risk

1. Unclear randomization process, and some imprecision of results and CI.

FAMCICLOVIR (5 DAYS) VERSUS FAMCICLOVIR (10 DAYS)

Quality assessment							No. of patients		Effect	Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Famciclovir 5 days	Famciclovir 10 days			
Duration of lesions from onset of treatment (assessed with: median time complete healing)											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	285	427	Median **7–8 days (similar)**	⨁⨁⨁◯ MODERATE	IMPORTANT
Pain – not measured											
Quality of life – not measured											
Adverse events – drug toxicity (assessed with: number of events)											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	285	427	Mild nausea and dizziness reported events with famciclovir	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of symptoms from onset of treatment (assessed with: time to loss of symptoms)											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	150	225	Median **6–8 days for 5 days** and **8–12 days for 10 days** (similar)	⨁⨁⨁◯ MODERATE	IMPORTANT
HSV-2 transmission – not measured											
Compliance – not measured											
Duration of viral shedding (median time to cessation viral shedding)											
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	207	348	Median **2–3 days (similar)**	⨁⨁⨁◯ MODERATE[1]	IMPORTANT

CI: confidence intervals; MD: mean difference; RR: relative risk

1. Unclear randomisation process, and some imprecision of results and CI.

ACICLOVIR HIGH DOSE VERSUS ACICLOVIR LOW DOSE

Wald 1994	High dose aciclovir (4 g daily × 10 days)	Standard dose aciclovir (1 g daily × 10 days)

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aciclovir high dose	Aciclovir low dose	Relative (95% CI)	Absolute (95% CI)		
Duration of lesions from onset of treatment (assessed with: median time to resolution of all lesions)												
1	Randomized trials	Very serious[1]	Not serious	Not serious	Serious[2]	None	59	28	–	Median **1 day more**	⨁◯◯◯ VERY LOW	IMPORTANT
Pain												
1	Randomized trials	Very serious[1]	Not serious	Not serious	Serious[2]	None	59	28	–	Median **2 days fewer**	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life – not measured												
Adverse events – drug toxicity (assessed with: number of events)												
1	Randomized trials	Very serious[1]	Not serious	Not serious	Serious[2]	None	7/88 (8.0%)	0/41 (0.0%) 8.5%	**RR 7.08** (0.41–121.05)	517 more per 1000 (from 50 fewer to 1000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Time to first recurrence												
1	Randomized trials	Very serious[1]	Not serious	Not serious	Serious[2]	None	59	28	–	Median **8 days fewer** (11–196 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
HSV-2 transmission – not measured												
Compliance – not measured												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aciclovir high dose	Aciclovir low dose	Relative (95% CI)	Absolute (95% CI)		
Duration of viral shedding												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	59	28	–	Median **3 days for each dose**	⨁⨁◯◯ LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; RR: relative risk

1. Unclear randomization process, incomplete outcome data, difference in baseline characteristics, and considering imprecision
2. Few participants and results not precise

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Patient values and preferences, acceptability and cost: specific to herpes simplex virus infections

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RECOMMENDATION 3 AND 4

Should episodic therapy be used for the treatment of recurrent episodes of herpes simplex virus infections?	
Population:	Recurrent episodes of herpes simplex infections
Intervention:	Episodic therapy
Comparison:	No therapy and different dosages
Main outcomes:	**Critical:** HSV-2 transmission, HSV-2 shedding **Important:** HSV-2 severity/pain, quality of life, side-effects, compliance, ulcer healing, duration of clinical episode
Setting:	Outpatients
Perspective:	Patients
Background:	The herpes simplex virus (HSV), or herpes, is categorized into two types: herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2). Both HSV-1 and HSV-2 are highly infectious. HSV-1 is transmitted by oral-to-oral contact and mainly causes herpes labialis, or cold sores, but can also cause genital herpes. HSV-2 is an STI that can cause genital herpes. Most infections are transmitted via asymptomatic viral shedding. Oral antiviral medications are available for initial, episodic and suppressive therapy; however, there is no cure for the infection. The medications vary: aciclovir, famciclovir and valaciclovir. In 2003, WHO guidelines recommended dosages for: aciclovir, 200 mg orally, 5 times daily for 5 days; aciclovir, 400 mg orally, 3 thrice daily for 5 days; aciclovir, 800 mg orally, twice daily for 5 days; valaciclovir, 500 mg orally, twice daily for 5 days; valaciclovir, 1000 mg orally, once daily for 5 days; OR famciclovir, 125 mg orally, twice daily for 5 days. The Guideline Development Group (GDG) identified the above treatments for review.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Globally in 2012, it was estimated that over 417 million people were currently infected with HSV-2. For new infections in people 15–49 years old (2012), it was estimated at 19.2 million, of whom 11.8 million were women and 7.4 million were men. Estimates are heterogeneous across regions, but typically greater in low- and middle-income countries (with the exception of the USA). Recurrent episodes are caused by HSV reactivation. Recurrent episodes can occur in 20% to 50% of people, and the median recurrence rate is four in the first year. The rate of recurrence usually decreases over time but increases in about one quarter of patients. Immunosuppressed patients have more severe and frequent recurrences. Infection with HSV-2 also may increase the risk of acquiring an HIV infection. Moreover, HSV-2 can be transmitted to neonates from an infected pregnant mother.
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • Large • Varies • **Don't know**	**Research evidence:** We included thirteen reports of 16 RCTs that compared treatment with no treatment and compared different drugs and different dosages: Reichman 1982, Reichman 1984, Goldberg 1986, Sacks 1996, Spruance 1996, Tyring 1998, Wald 2002, Aoki 2006, Fife 2008, Paz-Bailey 2009, Leone Abudalu 2010, Phiri 2010, and Baeten 2012. Of the studies comparing to placebo, there were aciclovir (9 trials), valaciclovir (3 trials) and famciclovir (5 trials). We found 1 systematic review and used it to verify the included studies (Le Cleach et al., 2014). The summary of the findings for treatment to no treatment and different drugs and different dosages are in the evidence tables. **Additional considerations:** Aciclovir in various dosages for 2 to 5 days probably reduces the duration of viral shedding (MD: 1.32 fewer days; 95% CI: 1.36 to 1.27 fewer), symptoms (MD: 2.02 fewer days; 95% CI: 3.27 to 0.77 fewer) and lesions (MD: 1.07 fewer days; 95% CI: 1.3 to 1.0 fewer) when compared to placebo. Valaciclovir probably reduces the duration of viral shedding by a median of 2 days, and lesions and symptoms by 1–2 days when compared to placebo. Famciclovir probably reduces the duration of viral shedding, lesions and symptoms by a median of 1–2 days when compared to placebo. The GDG agreed that the benefits were small and the harms trivial between drugs and no treatment. In most trials, quality of life, compliance, pain, HSV-2 transmission, and HIV acquisition and transmission were not measured. Different dosages of aciclovir, valaciclovir and famciclovir were compared with each other. Two trials compared aciclovir and valaciclovir and found that there were probably little-to-no differences for duration of viral shedding, lesions, symptoms and adverse events (moderate quality evidence). One trial compared aciclovir to famciclovir and found that there was little-to-no difference for outcomes (low quality evidence). Another trial compared famciclovir to valaciclovir and found that there were probably little-to-no differences for outcomes (moderate quality evidence). The GDG agreed that there were trivial differences in benefits and harms among treatments. Different dosages of aciclovir were compared in two trials (200 mg 5 × a day for 5 days versus alternatives). There may be little-to-no difference between the doses for outcomes. Different dosages of valaciclovir were compared in 4 trials (500 mg twice a day × 5 days versus alternatives). There were probably little-to-no differences between the doses for outcomes. Famciclovir at 125, 250 or 500 mg twice daily × 5 days were compared, and there may be little-to-no differences in outcomes across the different dosages. Three studies compared aciclovir to placebo in people living with HIV, and two studies compared different doses of aciclovir, valaciclovir and famciclovir. The effects were inconsistent across different doses, but most doses were provided for 5 days resulting in benefits and few harms.
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	

Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • Low • **Moderate** • High • No included studies	**Research evidence:** No research evidence was identified. **Additional considerations:** The quality of the evidence for treatment of infrequent recurrent HSV-2 infection compared to no treatment was of moderate quality due to unclear randomization methods and/or unclear loss to follow-up in the trials. For comparisons of different drugs and dosages, the quality of the evidence was also moderate.
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • Possibly important uncertainty or variability • **Probably no important uncertainty or variability** • No important uncertainty or variability	**Research evidence:** A discrete choice exercise suggested subjects' preferences were influenced by both the treatment they follow and attributes of treatment including cost. Of all the attributes, patients place high value in unit change in chance of recurrence (1%), followed by unit change in number of tablets taken daily (1 tablet), unit change in chance of becoming infected with HIV, unit change in number of tablets taken in addition during each recurrence. In addition, qualitative studies suggested stigma related was also important. **Additional considerations:** None
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • **Does not favour either the intervention or the comparison** • Probably favours the intervention • Favours the intervention • Varies • Don't know	**Research evidence:** No research evidence was identified. **Additional considerations:** The GDG agreed that there would be little variability. However, it may be dependent on the severity of the recurrent episodes (this would be covered in recommendations for recurrent episodes that are frequent or severe).

Resources required

How large are the resource requirements (costs)?

- Large costs
- **Moderate costs**
- Negligible costs and savings
- Moderate savings
- Large savings
- Varies
- Don't know

A	B	C	D	E	F
Aciclovir 200 mg po	5	5 days	$0.05	$1.25	$1.56
Aciclovir 400 mg po	3	3–5 days	$0.04	$0.36 to $1.00	$0.45 to $1.25
Aciclovir 800 mg po	2	5 days	n.a.	n.a.	n.a.
Aciclovir 800 mg po	3	2 days	n.a.	n.a.	n.a.
Valaciclovir 500 mg	2	3–5 days	$0.625	$3.75 to $6.25	$4.68 to $7.80
Valaciclovir 1 g po	2	3–5 days	n.a	n.a	n.a
Famciclovir 125 mg po	2	5 days	n.a.	n.a.	n.a
Famciclovir 1 g po	2	1 days	n.a.	n.a.	n.a.

Sources: International drug price indicator guide (MSH, 2015) and www.drugs.com
A: treatment; B: dose per day; C: treatment duration; D: drug cost, per dose; E: drug cost per full-course treatment; F: 25% procurement as defined by *International drug price indicator guide* (MSH, 2015).
po: orally

Additional considerations:
The GDG agreed that the costs were cost of treatment per episode, not the absolute cost of treatment. The costs were moderate for aciclovir but increase due to recurrence, **were greater for valaciclovir and greater for famciclovir.**

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

- Very low
- Low
- Moderate
- High
- **No included studies**

Research evidence:
No research evidence was identified.

Additional considerations:
None

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

- Favours the comparison
- Probably favours the comparison
- **Does not favour either the intervention or the comparison**
- Probably favours the intervention
- Favours the intervention
- Varies
- No included studies

Research evidence:
No research evidence was identified.

Additional considerations:
The GDG agreed that there are small benefits with the drugs and moderate costs; less cost effectiveness with valaciclovir and famciclovir. Overall, the GDG agreed that cost effectiveness did not favour either of the drugs.

Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence:** No research evidence was identified. **Additional considerations:** The GDG discussed the proposition that a recommendation would reduce equity as it might decrease the amount of the drug available for primary infections, which has been highlighted as a priority due to more severe symptoms and sequelae. Overall, the GDG decided that there was probably no impact on equity. However, equity may be reduced when using the more costly valaciclovir and famciclovir.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • Yes • **Varies** • Don't knows	**Research evidence:** We searched for reviews and studies specific to herpes treatment acceptability. A systematic review of the literature for treatment utilization in STIs (in India) reported that utilization ranged from 16% to 55% in the community-based studies, and was higher (~70%) in research trials. Treatment might not be acceptable to patients due to the resources and availability of services, social factors and distance. Non-utilization was also due to ignorance, illiteracy and lack of awareness; and women reported a lack of female doctors, being afraid of results and judgement of doctors, stigma, shyness and embarrassment. Cost of care and less faith in clinical care were also factors. An overview of reviews of medication adherence (Ryan, 2014) reported that adherence might be improved with simpler drug regimens. However, when compliance was measured in the studies included for HSV treatments, compliance was similar among drugs. **Additional considerations:** Given the nature of the course of treatment, the GDG discussed that aciclovir might be more acceptable. Valaciclovir might be more acceptable to patients who can afford it, but it may be unacceptable to those who cannot afford it. Therefore, the acceptability varies across settings. The same conclusions were reached for famciclovir.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** No research evidence was identified. **Additional considerations:** The treatment was considered widely available, but cost was still a concern. Additionally, there was concern that the drug might not be paid for by health systems or donors as the infection was considered recurrent. The GDG also discussed that treatment could be more effective if it were available for administration to a patient at the earliest stages of symptoms, rather than having to wait until they could see a clinician for their treatment. Thus, group members suggested that the recommendation recognize that benefits could be maximized if this opportunity to operationalize pharmacy workers to provide drugs is taken.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Should episodic therapy be used for the treatment of recurrent episodes of herpes simplex virus type 2 infections?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Recommendation	The GDG had a vote, which resulted (14 for; 6 against) in favouring a conditional recommendation of using aciclovir for treatment of recurrent infections over no treatment. There was a GDG vote (12 for; 9 against) that there would be a conditional recommendation for the use of valaciclovir, the primary condition being that of cost. **Recommendation 3:** For adults and adolescents with a recurrent clinical episode of genital HSV infection, the WHO STI guideline suggests treatment over no treatment. *Conditional recommendation, moderate quality evidence* **Remarks:** Treatment should be given within the first 24 hours of the onset of symptoms or during the prodromal phase. This recommendation also applies to people living with HIV, people who are immunocompromised and pregnant women. **Recommendation 4:** For adults and adolescents with a recurrent clinical episode of genital HSV infection, the WHO STI guideline suggests the use of aciclovir over valaciclovir or famciclovir. *Conditional recommendation, moderate quality evidence* Dosages for adults, adolescents and pregnant women: • aciclovir 400 mg orally thrice daily for 5 days, 800 mg twice daily for 5 days, or 800 mg thrice daily for 2 days • valaciclovir 500 mg orally twice daily for 3 days • famciclovir 250 mg twice daily for 5 days Dosages for people living with HIV and people who are immunocompromised: • aciclovir 400 mg orally thrice daily for 5 days • valaciclovir 500 mg orally twice daily for 5 days • famciclovir 500 mg orally twice daily for 5 days **Remarks:** Although the benefits of the medicines are probably similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of dosage may depend on compliance considerations. Treatment should be given within the first 24 hours of the onset of symptoms or during the prodromal phase.				

CONCLUSIONS

Should episodic therapy be used for the treatment of recurrent episodes of herpes simplex virus type 2 infections?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Justification	The evidence for treatment of recurrent clinical episodes of genital HSV infection that are not frequent compared to no treatment is of moderate quality, due to unclear randomization methods and/or unclear loss to follow-up in the trials. Data from 16 randomized controlled trials were reported in 13 articles, relating to the use of aciclovir (9 trials), valaciclovir (3 trials) and famciclovir (5 trials). The findings indicate that aciclovir in various dosages for 2–5 days probably reduces the duration of viral shedding (MD: 1.32 fewer days; 95% CI: 1.36–1.27), symptoms (MD: 2.02 fewer days; 95% CI: 3.27–0.77) and lesions (MD: 1.07 fewer days; 95% CI: 1.3–1.0) when compared to placebo. Valaciclovir in various dosages probably reduces the duration of viral shedding by a median of 2 days, and lesions and symptoms by 1–2 days when compared to placebo. Famciclovir in various dosages probably reduces the duration of viral shedding, lesions and symptoms by a median of 1–2 days when compared to placebo. The GDG agreed that the differences in benefits were small and the differences in harms were trivial between the medicines and no treatment. In most trials, quality of life, compliance, pain, genital HSV transmission, and HIV transmission and acquisition were not measured. Aciclovir, valaciclovir and famciclovir were compared. Two trials compared aciclovir and valaciclovir and found that there is probably little to no difference between the two medicines in terms of duration of viral shedding, lesions and symptoms, and risk of adverse events (moderate quality evidence). One trial compared aciclovir to famciclovir and found that there may be little to no difference in the same outcomes (low quality evidence). Another trial compared famciclovir to valaciclovir and found that there is probably little to no difference in outcomes (moderate quality evidence). The GDG agreed that there were only trivial differences in benefits and harms between the medicines. Different dosages of aciclovir were compared in two trials (200 mg five times daily for 5 days versus alternatives). The findings indicate that there may be little to no difference between the various doses in terms of duration of symptoms, lesions and viral shedding, and adverse events. Different dosages of valaciclovir were compared in four trials (500 mg twice daily for 5 days versus the same for 3 days, and versus 1000 mg twice daily for 5 days). Again findings indicate there is probably little to no difference in outcomes between the doses. Famciclovir at doses of 125, 250 or 500 mg twice daily for 5 days were compared and there may be little to no difference in outcomes across these different dosages. There were data providing moderate to low quality evidence from three studies that compared aciclovir to placebo in people living with HIV, and two studies that compared different doses of aciclovir, valaciclovir and famciclovir. The effects were inconsistent across different doses, but most doses were provided for 5 days and generally resulted in benefits and few harms. The GDG agreed that there would be little variability in patient values and preferences relating to the different medicines and treatment regimens. However, higher value is likely to be placed on reducing the number and frequency of tablets taken. Research relating to other conditions indicates that adherence to treatment regimens may be improved with simpler regimens, although when compliance was measured in the studies included for HSV treatments, compliance was similar between different medicines and treatment regimens. Overall, it was agreed that the different regimens and medicines are probably acceptable to most people. Since the comparisons of different dosages of medicines compared to placebo and to each other showed few differences, the GDG agreed to recommend the dosages and regimens requiring fewer days of treatment and fewer tablets per day. Both valaciclovir and famciclovir are more expensive than aciclovir, and famciclovir is more expensive than valaciclovir. Where the medicines are a direct cost to people with HSV, the more expensive medicines would probably reduce equity if recommended.				

Should episodic therapy be used for the treatment of recurrent episodes of herpes simplex virus type 2 infections?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Justification	In summary, there are probably small benefits and trivial side-effects of episodic therapy over no treatment, and moderate additional costs of providing episodic treatment versus no treatment. There may be trivial differences in benefits and side-effects between the different medicines and dosages. Although there is probably no important uncertainty or variability in the values patients place on reducing the duration of lesions and other symptoms, acceptability of episodic therapy may depend on the individual. All medicines are feasible to provide, but aciclovir costs less than famciclovir or valaciclovir.				
Subgroup considerations	This recommendation also applies to people living with HIV, people who are immunocompromised and pregnant women.				
Implementation considerations	Treatment should be started at the onset of symptoms and choice of dosage may depend on individual compliance.				
Monitoring and evaluation					
Research priorities	Little evidence was found for outcomes critical to making decisions about drugs to treat first or recurrent episodes of genital HSV infections. Important patient outcomes should be measured in clinical trials, such as genital HSV acquisition and transmission, HIV acquisition and transmission, quality of life and pain. There were few available data for direct comparisons of different drugs, in particular for comparisons with famciclovir. There were also few studies comparing the different dosages of the drugs. Future research could use the dosages recommended in these guidelines as comparators. Equity issues, acceptance of and compliance with different drugs and regimens should also be explored in people with genital HSV infections. Although this search was not limited to different populations, there were few data for key populations, such as people with HIV infection, people who are immunocompromised and pregnant women. More information can also be provided to allow for the critical appraisal of clinical trials by following the standards of reporting of RCTs, in particular for the methods of randomization and allocation concealment and blinding.				

EVIDENCE TABLES

Aciclovir versus placebo

Study	Dosage
Baeten 2012	aciclovir 400 mg orally 3 × daily × 5 days
Goldberg 1986 group A	aciclovir 800 mg 2 × daily × 5 days
Goldberg 1986 group B	aciclovir 200 mg 5 × daily × 5 days
Paz Bailey 2009	aciclovir 400 mg 3 × daily × 5 days
Phiri 2010	aciclovir 800 mg 2 × daily for 5 days
Reichman 1982 study A	aciclovir 200 mg 5 × daily × 5 days
Reichman 1982 study B	aciclovir 200 mg 5 × daily × 5 days
Tyring 1998	aciclovir 200 mg 5 × daily × 5 days
Wald 2002	aciclovir 800 mg 3 × daily × 2 days

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Episodic aciclovir	Placebo	Relative (95% CI)	Absolute (95% CI)		
Duration of viral shedding (assessed with: days)												
5	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	792	440	–	MD **1.32 days fewer** (1.36–1.27 fewer)[2]	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of symptoms from onset of treatment (assessed with: days)												
4	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	657	262	–	MD **2.02 days fewer** (3.27–0.77 fewer)[2]	⨁⨁⨁◯ MODERATE	IMPORTANT
Duration of lesions from onset of treatment												
9	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	991	551	–	MD **1.07 days fewer** (1.13–1.00 fewer)[3]	⨁⨁⨁◯ MODERATE	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Episodic aciclovir	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life – not measured												
Compliance – not measured												
HSV-2 severity/pain – not measured												
HSV-2 transmission – not measured												
HIV transmission and acquisition – not measured												
Adverse event – any adverse event												
5	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	65/555 (12.1%)	34/445 (7.6%)	**RR 1.20** (0.61–2.35)	15 more per 1000 (from 30 fewer to 103 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: confidence intervals; MD: mean difference; RR: relative risk

1. Most studies had unclear randomization or unclear loss to follow-up.
2. Two of the studies (Tyring 1998 and Wald 2002) reported median values consistent with the pooled mean difference.
3. Four of the studies reported median values and results are consistent.

VALACICLOVIR VERSUS PLACEBO

Study	Dosage
Spruance 1996 group A	valaciclovir 1 g 2 × daily × 5 days
Spruance 1996 group B	valaciclovir 500 mg 2 × daily × 5 days
Tyring 1998	valaciclovir 1000 mg 2 × daily × 5 days

Quality assessment							Impact	Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Duration of viral shedding									
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	Median values for people (1040) receiving valaciclovir was 2 days and receiving placebo (441) was 4 days. 1 study (694 people) also reported HR 2.55 (1.91–3.40) with placebo.	⨁⨁⨁◯ MODERATE	CRITICAL
HSV-2 transmission – not measured									
Duration of lesions from onset of treatment (assessed with: days)									
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	Median values for people (1040) receiving valaciclovir ranged from 4–5 days and with placebo (441) was 6 days.	⨁⨁⨁◯ MODERATE	IMPORTANT
Duration of symptoms from onset of treatment (assessed with: days)									
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	Median values for people (1040) receiving valaciclovir ranged from 4–5 days and with placebo (441) was 5.9 days.	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life – not measured									
Compliance – not measured									
Adverse events									
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	1 study (787) reported similar adverse events across groups. Another study reported 4/512 with a serious adverse events with valaciclovir and 1/182 with placebo.	⨁⨁⨁◯ MODERATE	IMPORTANT
Specific adverse events - see forest plots									

CI: confidence intervals; MD: mean difference; RR: relative risk

1. Unclear blinding or randomization in most studies, or lost to follow-up.

FAMCICLOVIR VERSUS PLACEBO

Study	Dosage
Sacks 1996 group A	famciclovir 125 mg 2 × daily × 5 days
Sacks 1996 group B	famciclovir 250 mg 2 × daily × 5 days
Sacks 1996 group C	famciclovir 500 mg 2 × daily × 5 days
Aoki 2006	famciclovir 1000 mg 2 × daily × 1 day
Leone 2010	famciclovir 1000 mg 2 × daily × 1 day

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	episodic famciclovir	Placebo	Relative (95% CI)	Absolute (95% CI)		
Duration of viral shedding												
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	1 article reported 3 separate analyses (669 participants): median number of days 1.3–1.7 days with famciclovir and 3.4 days with placebo.				⨁⨁⨁◯ MODERATE	CRITICAL
HSV-2 transmission – not measured												
Duration of lesions from onset of treatment												
5	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	Median duration was reported and ranged from 3.5–5.38 with famciclovir (730 participants); and 4.8–5 days with placebo (567 participants).				⨁⨁⨁◯ MODERATE	IMPORTANT
Duration of symptoms from onset of treatment												
5	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	Median duration was reported and ranged from 3.1–4.5 days with famciclovir (730 participants); and 3.7–5.7 days with placebo (567 participants).				⨁⨁⨁◯ MODERATE	IMPORTANT
Compliance – not measured												
Quality of life – not measured												
HSV-2 severity/pain – not measured												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	episodic famciclovir	Placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events (serious and non-serious)												
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	269/572 (47.0%)	71/199 (35.7%)	**RR 1.14** (0.95–1.36)[2]	50 more per 1000 (from 18 fewer to 128 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: confidence intervals; MD: mean difference; RR: relative risk

1. Unclear blinding or randomization in most studies, or lost to follow-up.
2. 1 study (n=329) reported similar non-serious adverse events in both groups and no serious adverse events.

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EPISODIC ACICLOVIR VERSUS NO TREATMENT FOR PEOPLE LIVING WITH HIV

Efficacy of aciclovir for episodic therapy versus no treatment for people living with HIV											
Quality assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no treatment	With aciclovir		Risk with no treatment	Risk difference with episodic drug
Aciclovir 800 mg twice daily × 5 days vs placebo: number of people healed (ulcer healing)											
215 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	87/107 (81.3%)	91/108 (84.3%)	**RR 1.04** (0.92–1.17)	813 per 1000	**33 more per 1000** (65 fewer to 138 more)
Aciclovir 800 mg twice daily × 5 days vs placebo: side-effects											
371 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	11/187 (5.9%)	19/184 (10.3%)	**RR 1.76** (0.86–3.59)	59 per 1000	**45 more per 1000** (8 fewer to 152 more)
Aciclovir 400 mg 3 times daily × 5 days vs placebo: number of people healed (ulcer healing)											
721 (2 RCTs)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	165/365 (45.2%)	158/356 (44.4%)	**RR 0.99** (0.84–1.16)	452 per 1000	**5 fewer per 1000** (72 fewer to 72 more)
Aciclovir 400 mg 3 × daily × 5 days vs placebo: HIV viral load											
193 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	39/105 (37.1%)	21/88 (23.9%)	**RR 0.64** (0.41–1.01)	371 per 1000	**134 fewer per 1000** (219 fewer to 4 more)
Aciclovir 800 mg twice daily × 5 days vs placebo: HIV viral load											
1500 (3 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ MODERATE	Three studies reported that Plasma HIV-1 RNA among patients with detectable plasma HIV-1 RNA (measured at day 0 to day 28), mean (95% CI), log10 copies/ml: for aciclovir 4.85 (4.73–5.40) to 4.71 (5.10–5.50); for placebo 4.84 (4.71–5.50) to 4.85 (4.71–5.50)					

CI: confidence interval; RR: risk ratio

1. Considered with imprecise results since 95% CI includes potential for fewer or greater cures or adverse events and few events across studies

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EPISODIC ACICLOVIR VERSUS EPISODIC VALACICLOVIR

Bodsworth 1997	valaciclovir 500 mg 2 × daily × 5 days aciclovir 200 mg 5 × daily × 5 days	**Tyring 1998**	valaciclovir 1000 mg 2 × daily × 5 days aciclovir 200 mg 5 × daily × 5 days

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Episodic valaciclovir	Episodic aciclovir	Relative (95% CI)	Absolute (95% CI)		
Duration of viral shedding												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	1 study (1018 participants) reported median of 2 days of viral shedding across the 2 groups. Another study reported HR 0.97 (0.75–1.26) in favour of valaciclovir.				⨁⨁⨁◯ MODERATE	IMPORTANT
Viral shedding (number of people with at least one positive culture of lesion)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	330/890 (37%)	332/867 (38%)	**RR 0.97** (0.86–1.09)	11 per 1000 fewer (from 52 fewer to 33 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
HSV-2 transmission – not measured												
Duration of lesions from onset of treatment (assessed with: days)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	2 studies (1757 participants) reported median values across groups of 4.4–4.8 days.				⨁⨁⨁◯ MODERATE	CRITICAL
Duration of symptoms from onset of treatment (assessed with: days)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	2 studies (1757 participants) reported median values across all groups of 4.6–4.8 days.				⨁⨁⨁◯ MODERATE	CRITICAL
HSV-2 severity/pain – not measured												
Quality of life – not measured												
Compliance – not measured												
Adverse events (serious)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[3]	None	1/890 (0.1%)	2/867 (0.2%)	**RR 0.32** (0.03–3.11)	1 fewer per 1000 (from 1 fewer to 2 more	⨁⨁⨁◯ MODERATE	IMPORTANT

MD: mean difference; HR: hazard ratio; RR: relative risk.

1. Unclear randomization methods or incomplete data from studies

EPISODIC ACICLOVIR VERSUS EPISODIC FAMCICLOVIR

Chodisow 2001	aciclovir 200 mg 5 × daily × 5 days famciclovir 125 mg twice daily × 5 days

Quality assessment							Effect		No. of patients		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Episodic aciclovir**	**Episodic famciclovir**	**Relative (95% CI)**	**Absolute (95% CI)**		
Duration of viral shedding – not measured												
HSV-2 transmission – not measured												
Duration of lesions from onset of treatment (assessed with: days)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[1]	None	97	107	–	MD **0.25 days more** (0.3 more to 0.8 fewer)	⨁⨁◯◯ LOW	CRITICAL
Duration of symptoms from onset of treatment – not measured												
HSV-2 severity/pain – not measured												
Quality of life – not measured												
Compliance												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[1]	None	1 study with 204 participants reported comparable compliance with only 5 people in each group with less than 80% compliance				⨁⨁◯◯ LOW	IMPORTANT
Adverse events (non-serious and serious)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[1]	None	1 study with 204 participants reported that non-serious adverse events did not differ between groups and included headache, nausea and gastrointestinal events. 4/107 participants receiving aciclovir reported serious adverse events, while none were reported with famciclovir.				⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; MD: mean difference

1. Method of randomization and allocation unclear, and approximately 10% of participants lost to follow-up – downgraded with imprecision due to few participants.

EPISODIC VALACICLOVIR VERSUS EPISODIC FAMCICLOVIR

Abudalu 2008	famciclovir 1000 mg 2 × daily × 1 day valaciclovir 500 mg 2 × daily × 3 days

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Episodic valaciclovir	Episodic famciclovir	Relative (95% CI)	Absolute (95% CI)		
HSV-2 transmission – not measured												
Duration of viral shedding – not measured												
Duration of lesions from onset of treatment (assessed with: days)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	1 study (651 participants) reported median of 3.01 for valaciclovir and 3.07 for famciclovir.				⨁⨁⨁◯ MODERATE	CRITICAL
Duration of symptoms from onset of treatment												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	1 study (651 participants) reported median of 3.0 for valaciclovir and 3.03 for famciclovir.				⨁⨁⨁◯ MODERATE	CRITICAL
HSV-2 severity/pain – not measured												
Quality of life – not measured												
Compliance												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	Adherence to study medication as prescribed was excellent, with 97.6% of famciclovir-treated patients (362 of 371 patients) receiving 2 doses on day 1 and 92.2% of valaciclovir-treated patients (355 of 385 patients) receiving all 6 doses over 3 days.				⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events – not serious												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	86/385 (22.3%)	86/371 (23.2%)	**RR 0.96** (0.74–1.25)		⨁⨁⨁◯ MODERATE	IMPORTANT

MD: mean difference; RR: relative risk

1 Method of randomization and allocation unclear, and approximately 10% did not complete study.

EPISODIC ACICLOVIR VERSUS EPISODIC ACICLOVIR

Goldberg 1986	aciclovir oral 800 mg (4 capsules) 2 × daily × 5 days aciclovir 200 mg (1 capsule) 5 × daily × 5 days
Straus 1986	aciclovir 200 mg capsules 1 capsule 5 × daily × 5 days (daily group) aciclovir 400 mg capsules 1 capsule 3 × daily on weekend days only (weekend group)

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Episodic aciclovir 800 mg	Episodic aciclovir 200 mg	Relative (95% CI)	Absolute (95% CI)		
Duration of viral shedding – not measured												
Viral shedding (number of people with at least one positive culture of lesion) – not measured												
HSV-2 transmission – not measured												
Duration of lesions from onset of treatment (assessed with: days)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	81	40		MD **0.9 fewer** (1.72 fewer to 0.08 fewer)	⨁⨁◯◯ LOW	CRITICAL
Duration of symptoms from onset of treatment (assessed with: days)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	77	37		MD **0.6 fewer** (1.54 fewer to 0.34 more)	⨁⨁◯◯ LOW	CRITICAL
Proportion of patients with recurrent herpes while therapy												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	3/18 (16.7%)	13/17 (76.5%)	RR 0.22 (0.08–0.63)	**596 fewer per 1000** (from 285–704 fewer)	⨁⨁◯◯ LOW	IMPORTANT
HSV-2 severity/pain – not measured												
Quality of life – not measured												
Compliance												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	1 study (121 participants) reported that with daily treatment compliance was excellent				⨁⨁◯◯ LOW	IMPORTANT

MD: mean difference; RR: relative risk

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Episodic aciclovir 800 mg	Episodic aciclovir 200 mg	Relative (95% CI)	Absolute (95% CI)		
Adverse events (diarrhoea) - see forest plots for other side-effects												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	3/18 (16.7%)	7/17 (41.2%)	RR 0.40 (0.12–1.32)	247 fewer per 1000 (from 132 more to 362 fewer)	⨁⨁◯◯ LOW	IMPORTANT

MD: mean difference; RR: relative risk

1. Unclear randomization process, and some imprecision of results and confidence intervals.
2. Few events to determine effect.

EPISODIC VALACICLOVIR VERSUS EPISODIC VALACICLOVIR

Leone 2002	valaciclovir 500 mg bid 5-day regimen valaciclovir 500 mg bid 3-day regimen	**Strand 2002**	valaciclovir 500 mg bid × 5-day regimen valaciclovir 500 mg bid × 3-day regimen
Saiag 1999	valaciclovir 1000 mg 1 × daily × 5-day regimen valaciclovir 500 mg bid × 5-day regimen	**Spruance 1996**	valaciclovir 1000 mg once daily × 5-day regimen valaciclovir 500 mg bid × 5-day regimen

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Episodic valaciclovir	Episodic valaciclovir	Relative (95% CI)	Absolute (95% CI)		
Duration of viral shedding												
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	2 studies (1259 participants) reported median values across groups of 1.7–2.0 days.				⨁⨁⨁◯ MODERATE	CRITICAL
Viral shedding (number of people with at least one positive culture of lesion) – not measured												
HSV-2 transmission – not measured												
Duration of lesions from onset of treatment (assessed with: days)												
4	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	4 studies (2630 participants) reported median values across groups of 3.4–4.9 days.				⨁⨁⨁◯ MODERATE	CRITICAL
Numbers of complete lesion healed												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	359/444 (80.9%)	77.8%	RR 1.04 (0.97–1.11)	31 more per 1000 (from 23 fewer to 86 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of symptoms from onset of treatment (assessed with: days)												
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	3 studies (1980 participants) reported median values across groups of 4.0–4.7 days.				⨁⨁⨁◯ MODERATE	CRITICAL
HSV-2 severity/pain (assessed with: days)												
4	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	4 studies (2902 participants) reported median values across groups of 2.5–3.0 days.				⨁⨁⨁◯ MODERATE	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Episodic valaciclovir	Episodic valaciclovir	Relative (95% CI)	Absolute (95% CI)		
Quality of life – not measured												
Compliance – not measured												
Adverse events (general) – see forest plots for individual side-effects												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	72/444 (16.2%)	83/478 (17.4%)	RR 0.93 (0.70–1.25)	12 fewer per 1000 (from 43 more to 52 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: confidence interval; RR: relative risk

1. Approximately 10% did not complete study; patients not likely blinded to length of regimen

EPISODIC FAMCICLOVIR VERSES EPISODIC FAMCICLOVIR

Sacks 1996	famciclovir 125 mg, 250 mg, 500 mg 2 × daily × 5 days
Sacks 2005	famciclovir 125 mg, 250 mg, 500 mg 2 × daily × 5 days

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Episodic famciclovir	Episodic famciclovir	Relative (95% CI)	Absolute (95% CI)		
Duration of viral shedding												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	2 studies (350 participants) reported median of 1.3–1.7 days of viral shedding across the 3 groups.				⨁⨁◯◯ LOW	CRITICAL
Viral shedding (number of people with at least one positive culture of lesion) – not measured												
HSV-2 transmission – not measured												
Duration of lesions from onset of treatment (assessed with: days)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	2 studies (350 participants) reported median of 3.7–4.4 days of lesion healed across the 3 groups.				⨁⨁◯◯ LOW	CRITICAL
Duration of symptoms from onset of treatment (assessed with: days)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	2 studies (184 participants) reported median of 3.8–4.4 days of duration of symptoms across the 3 groups.				⨁⨁◯◯ LOW	CRITICAL
HSV-2 severity/pain – not measured												
Quality of life – not measured												
Compliance – not measured												
Adverse events (not serious)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	1 study (229 participants) reported that number of patients with adverse events between 47–55 across the 3 groups.				⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: relative risk

1. Unclear randomization process, and some imprecision of results and CIs.
2. Few events to determine effect.

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EPISODIC THERAPY FOR PEOPLE LIVING WITH HIV

Efficacy of different treatments for episodic drugs for people living with HIV											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With aciclovir	**With comparison**		**Risk with aciclovir**	**Risk difference with comparison**
Valaciclovir at 1000 mg twice daily or aciclovir at 200 mg 5 × daily × 5 days: healing											
467 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	No differences were detected between the valaciclovir 1000 mg twice daily and aciclovir 200 mg 5 × daily regimens on episode duration or lesion healing. Lesions were observed to progress through all stages to healing in 394 of the 467 treated patients. The hazard ratio [CI] for valaciclovir vs aciclovir on lesion healing was 0.98 [0.79, 1.22], $P = 0.89$, and the median healing time was 5 days.				
Valaciclovir at 1000 mg twice daily or aciclovir at 200 mg 5 × daily × 5 days: side-effects											
467 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	92/237 (38.8%)	86/230 (37.4%)	**RR 0.96** (0.76–1.21)	**Moderate**	
										388 per 1000	**16 fewer per 1000** (93 fewer to 82 more)
Famciclovir 500 mg twice daily, or aciclovir 400 mg 5 × daily × 7 days: median time to complete healing of all lesions											
293 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	The median time to complete healing of all lesions was 7 days in both treatment groups with a hazard ratio of 1.01 (95% CI, 0.79±1.29; $P = 0.95$).				
Famciclovir 500 mg twice daily, or aciclovir 400 mg five times daily for 7 days: median time to cessation of viral shedding											
293 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	The median time to cessation of viral shedding from all lesions was 2 days for both famciclovir and aciclovir (hazard ratio, 0.93; 95% CI, 0.68±1.27; $P = 0.64$).				
Famciclovir 500 mg twice daily, or aciclovir 400 mg five times daily for 7 days: median time to loss of symptoms											
293 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	The median time to loss of all lesion associated symptoms was 4 days in both groups (hazard ratio, 0.99; 95% CI, 0.75±1.30; $P = 0.93$).				

Efficacy of different treatments for episodic drugs for people living with HIV											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With aciclovir	With comparison		Risk with aciclovir	Risk difference with comparison
Famciclovir 500 mg twice daily, or aciclovir 400 mg five times daily for 7 days: side-effects											
293 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	82/143 (57.3%)	81/150 (54.0%)	**RR 0.94** (0.77–1.16)	**Moderate**	
										573 per 1000	**34 fewer per 1000** (132 fewer to 92 more)

CI: confidence interval; RR: risk ratio

1. Considered with imprecise results since 95% CI includes potential for fewer or greater cures or adverse events and few events across studies

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RECOMMENDATION 5 AND 6

Should suppressive antiviral versus episodic antiviral be used for the treatment of frequent recurrent episodes of herpes simplex virus?	
Population:	Frequent recurrent episodes of herpes simplex virus
Intervention:	Suppressive antiviral
Comparison:	Episodic antiviral
Main outcomes:	**Critical:** Recurrent clinical episodes, HSV-2 severity/pain, quality of life, HSV-2 transmission, HSV-2 shedding **Important:** Side-effects, HIV acquisition and transmission, HIV viral load, compliance Add for pregnant women critical outcomes: Maternal outcomes (caesarean section), fetal outcomes (neonatal herpes, teratogenicity, fetal loss, toxicity, neonatal death)
Setting:	Outpatients
Perspective:	Population
Background:	The herpes simplex virus (HSV), or herpes, is categorized into two types: HSV-1 and HSV-2. Both HSV-1 and HSV-2 are highly infectious. HSV-1 is transmitted by oral-to-oral contact and mainly causes herpes labialis, or "cold sores", but can also cause genital herpes. HSV-2 is a sexually transmitted infection that can cause genital herpes. Most infections are transmitted via asymptomatic viral shedding. Oral antiviral medications are available for initial, episodic, and suppressive therapy; however, there is no cure for the infection. The medications vary: aciclovir, famciclovir and valaciclovir. In 2003, WHO guidelines recommended the following dosage regimens for episodic treatment of recurrent infection: aciclovir, 200 mg orally, 5 times daily for 5 days; aciclovir, 400 mg orally, 3 times daily for 5 days; aciclovir, 800 mg orally, twice daily for 5 days; valaciclovir, 500 mg orally, twice daily for 5 days; valaciclovir, 1000 mg orally, once daily for 5 days; OR famciclovir, 125 mg orally, twice daily for 5 days. For suppressive therapy, the recommended dosage regimens were: aciclovir, 400 mg, orally, twice daily, continuously; valaciclovir 500 mg, orally, once daily; valaciclovir 1000 mg orally, once daily; famciclovir, 250 mg orally, twice daily. The Guideline Development Group (GDG) identified the following treatments for review: **Episodic therapy:** Aciclovir 200 mg po 5×/d x 5 days Aciclovir 400 mg po tid × 3–5 days Aciclovir 800 mg po bid × 5 days Aciclovir 800 mg po tid × 2 days Valaciclovir 500 mg po bid × 3–5 days Valaciclovir 1 g po bid × 3–5 days Famciclovir 125 mg po bid × 5 days Famciclovir 1 g po bid × 1 day **Suppressive therapy:** Aciclovir 200 mg po qid Aciclovir 400 mg po bid Valaciclovir 500 mg po qd Valaciclovir 1 g po qd Famciclovir 250 mg po bid

bid: twice daily; po: orally; qd: once daily; qid: four times daily; tid: thrice daily

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Recurrent episodes of genital HSV-2 occur a median of 4 (women) to 5 (men) times during the first year. However, there is great variability in the frequency of recurrences, even during the first year. In a study of 457 persons with newly acquired HSV-2 infection, 38% had 6 or more recurrences and 20% had more than 10 recurrences during the first year. 14% of women and 26% of men had more than 10 recurrences and only 26% of women and 8% of men had no or 1 recurrence in the first year of infection. Subsequently, the frequency of episodes slowly decreases, with an average decrease of 2 recurrences between years 1 and 5 of infection. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med. 1994;121(11):847–54.
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** Data from one Cochrane systematic review was used: Le Cleach 2014. We included 14 RCTs: Straus 1984, Mattison 1988, Mertz 1988, Mostow 1988, Baker 1989, Patel 1997, Reitano 1998, Corey 2004, Sekhin 2004, Fife 2006, Fife 2007, Fife 2008, Bartlett 2008, and Celum 2008. In these studies, all groups received treatment for their recurrences, but between episodes, some received a placebo while others received an intervention. **Additional considerations:** Most studies included people with 4 or more recurrences per year for 6–12 months. The GDG agreed that there are large benefits with suppressive over episodic therapy. Six studies compared suppressive aciclovir (from 200 to 400 mg twice daily and 800 mg once daily) to episodic therapy (usually 200 mg 5 times daily for 5 days) and found clinical recurrence was probably delayed and experienced by fewer people with suppressive therapy, and probably few differences in side-effects or compliance. The number of lesions with viral shedding was also probably reduced. Seven studies compared suppressive therapy with valaciclovir (from 250 to 1000 mg per day) to episodic therapy with valaciclovir (500 mg twice daily for 5 days). Clinical recurrence was probably delayed and experienced by fewer people with suppressive therapy, and probably few differences in side-effects or compliance. There may also be fewer days of pain and fewer HSV-2 transmissions to partners. The number of lesions with viral shedding was also probably reduced. One study compared suppressive famciclovir (250 mg twice daily for 6 months) to episodic therapy and found clinical recurrence may be delayed and experienced by fewer people with suppressive therapy, and there may be little difference in quality of life, satisfaction with therapy, or side-effects. There were few studies that directly compared different dosages of a specific suppressive therapy. One study compared aciclovir at 200 mg twice daily to 200 mg five times daily. The quality of evidence was low quality for little-to-no differences in recurrence, compliance and side-effects. Two studies compared valaciclovir 500 mg daily to 1000–3000 mg daily. There was very low quality evidence for little-to-no difference in duration of episodes, HSV-2 shedding and side-effects, and moderate quality evidence for little-to-no difference in the number of people who experienced a recurrence (risk ratio: 1.04; 95% CI: 0.94–1.16). Three studies compared famciclovir at doses greater than 250 mg twice daily to 250 mg twice daily or less. The time to first recurrence was probably similar across doses with little-to-no difference in side-effects. There may be fewer episodes per month with greater than 250 mg twice daily and fewer days of HSV-2 shedding. One study compared suppressive therapy with valaciclovir to aciclovir and found that there may be little-to-no difference in outcomes. Another study compared famciclovir to valaciclovir and found that there is probably little-to-no difference in recurrences and may be little-to-no differences in side-effects and compliance, but there may be more days of HSV-2 shedding with famciclovir (risk ratio: 2.23; 95% CI: 1.18–4.89).
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	

Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • Low • **Moderate** • High • No included studies	**Research evidence:** No research evidence was identified. **Additional considerations:** Overall, when comparing suppressive to episodic therapy, the quality of the evidence was moderate. When comparing the different drugs and dosages of suppressive therapy, the quality of the evidence was low.
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • Possibly important uncertainty or variability • **Probably no important uncertainty or variability** • No important uncertainty or variability	**Research evidence:** A discrete choice exercise suggested subjects' preferences were influenced by both the treatment they follow and attributes of treatment including cost. Of all the attributes, patients place high value in unit change in chance of recurrence (1%), followed by unit change in number of tablets taken daily (1 tablet), unit change in chance of becoming infected with HIV, unit change in number of tablets taken in addition during each recurrence. In addition, qualitative studies suggested stigma related is also important. **Additional considerations:** The GDG agreed that, clinically, people value non-transmission as the priority, followed by non-recurrence. They agreed that these priorities probably did not significantly vary.
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • **Favours the intervention** • Varies • Don't know	**Research evidence:** No research evidence was identified. **Additional considerations:** The GDG agreed that suppressive therapy with any of the drugs was favoured over episodic therapy.

Resources required

How large are the resource requirements (costs)?

- **Large costs**
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Varies
- Don't know

Research evidence:
Cost for episodic therapy

A	B	C	D	E	F
Aciclovir 200 mg po	5	5 days	$0.05	$1.25	$1.56
Aciclovir 400 mg po	3	3–5 days	$0.04	$0.36–$1.00	$0.45–$1.25
Aciclovir 800 mg po	2	5 days	n.a.	n.a.	n.a.
Aciclovir 800 mg po	3	2 days	n.a.	n.a.	n.a.
Valaciclovir 500 mg	2	3–5 days	$0.625	$3.75–$6.25	$4.68–$7.80
Valaciclovir 1 g po	2	3–5 days	n.a	n.a	n.a
Famciclovir 125 mg po	2	5 days	n.a.	n.a.	n.a
Famciclovir 1 g po	2	1 day	n.a.	n.a.	n.a.

Cost for suppressive therapy per day

A	B	D	E	F
Aciclovir 200 mg po	4	$ 0.05	$0.20	$0.25
Aciclovir 400 mg po	2	$ 0.04	$0.08	$0.10
Valaciclovir 500 mg	1	$ 0.625	$0.625	$0.78
Valaciclovir 1 g po	1	n.a.	n.a.	n.a.
Famciclovir 250 mg po	2	$ 4.38	$8.76	$10.95

**Sources: International drug price indicator guide* (MSH, 2015) and www.drugs.com
A: treatment; B: dose per day; C: treatment duration; D: drug cost, per dose; E: drug per full-course treatment; F: 25% procurement as defined by *International drug price indicator guide* (MSH, 2015).
po: orally

Additional considerations:
The GDG was unable to determine the costs of suppressive therapy since costs were of individual dosages. The GDG agreed that the costs would be large.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

- Very low
- Low
- Moderate
- High
- **No included studies**

Research evidence:
No research evidence was available.

Additional considerations:
None

Cost effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • **No included studies**	**Research evidence:** No research evidence available. **Additional considerations:** The GDG agreed that the costs would likely be high for any of the drugs and depend on the setting. Although the cost may be high for an individual, there is a small population that would have frequent HSV-2 infections requiring suppressive therapy. There may also be a potential for cost savings in work productivity and health care use.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • **Varies** • Don't know	**Research evidence:** No research evidence available. **Additional considerations:** The impact on equity was unclear as HSV-2 occurs most in disadvantaged populations who may not have access to suppressive therapy; but with increasing access, equity could be increased. However, valaciclovir and famciclovir are more expensive than aciclovir and would probably reduce equity if recommended.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** An overview of reviews of medication adherence (Ryan, 2014) reported that adherence may be improved with simpler drug regimens. However, when compliance was measured in the studies included for HSV treatments, compliance was similar among drugs. **Additional considerations:** Many thought that some patients would be quite unwilling to take 2 pills per day for an extended time on suppressive therapy. Indeed, some physicians might be unwilling to administer this to many patients if compliance is going to be low. Additionally, the intervention may be unacceptable in terms of cost to whoever is paying for the drugs. Overall, it was agreed that the different regimens and drugs are probably acceptable to most people.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** No research evidence was identified. **Additional considerations:** Although the cost may be high for an individual, there is a small population that would have frequent HSV-2 infections requiring suppressive therapy. This would make it feasible to provide it to a small number of people. Follow-up may be difficult in some countries. It will also be important to define "frequent", and it was suggested that this varies by patient, and the recommendation should be flexible to take into consideration individual patient preferences.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Should suppressive antiviral versus episodic antiviral be used for the treatment of recurrent episodes of herpes simplex virus?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Recommendation	**Recommendation 5:** For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, the WHO STI guideline suggests suppressive therapy over episodic therapy, and reassessment after one year. *Conditional recommendation, moderate quality evidence* **Remarks:** Individuals who have frequent recurrences (e.g. 4–6 times a year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy. To determine frequency or severity, episodes can be monitored for the first few months. This recommendation also applies to people living with HIV, people who are immunocompromised and pregnant women. **Recommendation 6:** For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, the WHO STI guideline suggests aciclovir over valaciclovir or famciclovir for suppressive therapy. *Conditional recommendation, low quality evidence* Dosages for adults, adolescents and pregnant women: • aciclovir 400 mg orally twice daily • valaciclovir 500 mg orally once daily • famciclovir 250 mg orally twice daily Dosages for people living with HIV and people who are immunocompromised: • aciclovir 400 mg orally twice daily • valaciclovir 500 mg orally twice daily • famciclovir 500 mg orally twice daily **Remarks:** Individuals who have frequent recurrences (e.g. 4–6 times a year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy. To determine frequency or severity, episodes can be monitored for the first few months. Although the benefits of the medicines may be similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of medicine may also depend on compliance considerations.				
Justification	The evidence for suppressive therapy compared to episodic therapy of recurrent and frequent clinical episodes of genital HSV infection is of moderate quality for aciclovir therapies and valaciclovir therapies, but low quality for famciclovir therapies. Most studies included people with four or more recurrences per year and provided therapy for 6–12 months. The GDG agreed that there were large benefits with suppressive over episodic therapy and trivial differences in harms for people with frequently recurrent episodes of genital HSV infection. The GDG also agreed that treatment regimens including lower doses and fewer tablets should be recommended.				

Should suppressive antiviral versus episodic antiviral be used for the treatment of recurrent episodes of herpes simplex virus?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Justification	Six studies compared suppressive therapy with aciclovir (200 mg or 400 mg twice daily and 800 mg once daily) to episodic therapy with aciclovir (usually 200 mg five times daily for 5 days) and found that clinical recurrence is probably delayed and experienced by fewer people with suppressive therapy, with probably little difference in side-effects or compliance. The number of lesions with viral shedding is also probably reduced. Seven studies compared suppressive therapy with valaciclovir (250–1000 mg per day) to episodic therapy with valaciclovir (500 mg twice daily for 5 days). Clinical recurrence is probably delayed and experienced by fewer people with suppressive therapy, with probably little difference in side-effects or compliance. There may also be fewer days of pain and fewer genital HSV transmissions to partners. The number of lesions with viral shedding is also probably reduced. One study compared suppressive therapy with famciclovir (250 mg twice daily for 6 months) to episodic therapy with famciclovir (125 mg twice daily for 5 days) and found that clinical recurrence may be delayed and experienced by fewer people with suppressive therapy, and there may be little difference in quality of life, satisfaction with therapy, or side-effects. Few studies directly compared different dosages of a specific suppressive therapy. One study compared aciclovir at 200 mg twice daily to 200 mg five times daily. The quality of evidence was low; the findings indicated little to no difference in recurrence, compliance or side-effects. Two studies compared valaciclovir 500 mg daily with 1000–3000 mg daily. There was very low quality evidence for little to no difference in the duration of episodes, genital HSV shedding and side-effects; and moderate quality evidence for little to no difference in the number of people who experienced a recurrence (risk ratio: 1.04; 95% CI: 0.94–1.16). Three studies compared famciclovir at doses greater than 250 mg twice daily to doses of 250 mg or less twice daily. The time to first recurrence is probably similar across doses with little to no difference in side-effects. There may be fewer episodes per month with the higher dose regimen, as well as fewer days of genital HSV shedding. One study compared suppressive therapy with valaciclovir to aciclovir and found that there may be little to no difference in outcomes. Another study compared famciclovir to valaciclovir and found that there is probably little to no difference in recurrences and there may also be little to no difference in side-effects and compliance, but there may be more days of genital HSV shedding with famciclovir (risk ratio: 2.23; 95% CI: 1.18–4.89). For people living with HIV, there is moderate to low quality evidence from 13 studies reporting various outcome measures. There may be more benefits with treatment versus no treatment and the results were similar across different medicines and dosages. Medicines and dosages evaluated were aciclovir 400 mg orally twice daily, valaciclovir 500 mg orally twice daily (or 1000 mg once daily), and famciclovir 500 mg orally twice daily. The GDG agreed to recommend these doses as there is experience with them. The GDG agreed that there is probably no variability in patient values and preferences relating to the different medicines and treatment regimens. However, higher value is likely placed on avoiding genital HSV transmission (but there were few data) and reducing the number and frequency of tablets taken. Research relating to other conditions indicates that adherence may be improved with simpler medicine regimens, although when compliance was measured in the studies included for HSV treatments, compliance was similar between medicines. Overall, it was agreed that the different regimens and medicines are probably acceptable to most people. Since the comparisons of different dosages of medicines to placebo and to each other showed only small differences, the GDG agreed to recommend the dosages and regimens requiring fewer days of treatment and fewer tablets per day. There were no included studies for cost–effectiveness, but the GDG agreed that the costs would likely be high for any of the medicines and that costs depend on the setting. Although the cost may be high for an individual, there is a small population with frequent clinical episodes of genital HSV infection requiring suppressive therapy. There may also be a potential for cost savings in terms of work productivity and health care use. The impact on equity was unclear as genital HSV infection occurs most in disadvantaged populations who may not have access to suppressive therapy. However, equity could be increased with improved access. Both valaciclovir and famciclovir are more expensive than aciclovir, and famciclovir is more expensive than valaciclovir. Where the medicines are a direct cost to people with HSV, the more expensive medicines would probably reduce equity if recommended.				

Should suppressive antiviral versus episodic antiviral be used for the treatment of recurrent episodes of herpes simplex virus?					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Justification	In summary, the benefits of suppressive therapy over episodic therapy are probably large and the side-effects trivial. The medicines and treatment regimens are probably feasible and acceptable to individuals, but there are large costs with suppressive therapy, which may reduce equity between some populations. Less expensive medicines, such as aciclovir, may reduce the potential for this inequity.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	Little evidence was found for some outcomes critical to making decisions in trials comparing drugs to placebo or comparing different drugs to treat first or recurrent episodes of genital HSV infections. Important patient outcomes should be measured in clinical trials, such as genital HSV acquisition and transmission, HIV acquisition and transmission, quality of life and pain. There were few available data for direct comparisons of different drugs, in particular for comparisons with famciclovir. There were also few studies comparing the different dosages of the drugs. Future research could use the dosages recommended in these guidelines as comparators. Equity issues, acceptance of and compliance with different drugs and regimens should also be explored in people with genital HSV infections. Although this search was not limited to different populations, there were few data for key populations, such as people with HIV infection, people who are immunocompromised and pregnant women. More information can also be provided to allow for the critical appraisal of clinical trials by following the standards of reporting of RCTs, in particular for the methods of randomization and allocation concealment and blinding.				

EVIDENCE TABLES

Suppressive aciclovir versus episodic aciclovir

	Suppressive	Episodic
Baker 1989	aciclovir 800 mg 1 × daily	aciclovir 200 mg 5 × daily × 5 days
Mattison 1988	aciclovir 200 mg 2 × daily	aciclovir 200 mg 5 × daily × 5 days
Mertz 1988	aciclovir 400 mg 2 × daily × 1 year	aciclovir 200 mg 5 × daily × 5 days
Straus 1984	aciclovir 200 mg 3 × daily × 35 days	aciclovir 200 mg 5 × daily × 5 days
Sacks 1988	aciclovir 200 mg 3 × daily × 6 months	aciclovir 200 mg 5 × daily × 5 days
Celum 2008	aciclovir 400 mg 2 × daily × 12–18 months	aciclovir 400 mg 3 × daily × 5 days

Quality assessment							No. of patients	Effect			Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Suppressive antiviral	Episodic antiviral	Relative (95% CI)	Absolute (95% CI)		
Time to first recurrent episode												
5	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	No. of people: Suppressive 737, episodic: 449. In 2 trials with suppressive 400 mg × 2 or 800 mg daily, mean or median time was ~250 days, and 18 days with episodic. 3 trials with < 800 mg daily, time ranged from 72–250 days.				⨁⨁⨁◯ MODERATE	CRITICAL
Mean number of recurrence/month												
6	Randomized trials	Serious[1]	Not serious	Serious[2]	Not serious	None	No. of people: Suppressive 2380, episodic 2277. In 2 trials with suppressive 400 mg × 2 or 800 mg daily, mean number per month was 0.18, and 0.72–0.95 with episodic. 3 trials with < 800 mg daily ranged from 0.02–0.37				⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							No. of patients	Effect			Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Suppressive antiviral	Episodic antiviral	Relative (95% CI)	Absolute (95% CI)		
Number of participants with at least one clinical recurrence												
5	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	363/650 (55.8%)	547/561 (97.5%)	**RR 0.57** (0.53–0.61)[3]	419 fewer per 1000 (from 380–458 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Number of lesions with viral shedding (assessed with viral cultures and PCR – HSV DNA)												
2	Randomized trials	Serious[1,2]	Not serious	Not serious	Not serious	None	Largest study (1664 lesions analysed) found **RR 0.70 (0.62–0.78)** meaning 173 fewer per 1000 (from 127–219 fewer). Small study with 133 lesions analysed found **RR 0.28 (0.04–1.87).**				⨁⨁⨁◯ MODERATE	IMPORTANT
HSV-2 severity/pain – not measured												
HSV-2 transmission – not measured												
Quality of life – not measured												
Side-effects (serious – not considered related to treatment – death, hospitalization) – see details in additional table												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[4]	None	75/1637 (4.6%)	63/1640 (3.8%)	**RR 1.19** (0.86–1.66)	7 more per 1000 (from 5 fewer to 25 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Side-effects (not serious) – see details in additional table												
3	Randomized trials	Serious[1]	Not serious	Not serious	Serious[4]	None	31/178 (17.4%)	29/159 (18.2%)	**RR 1.07** (0.76–1.49)	16 more per 1000 (from 56 fewer to 113 more)	⨁⨁◯◯ LOW	IMPORTANT
								5.0%		4 more per 1000 (from 12 fewer to 25 more)		

Quality assessment							No. of patients	Effect			Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Suppressive antiviral	Episodic antiviral	Relative (95% CI)	Absolute (95% CI)		
Compliance												
3	Randomized trials	Not serious[1]	Not serious[5]	Not serious	Not serious	None	In 2 studies (~3400 people), compliance was similar in both groups. In another study (~47 people), a greater number of patients receiving episodic aciclovir were noncompliant.				⨁⨁⨁◯ MODERATE	IMPORTANT

CI: confidence interval; PCR: polymerase chain reaction; RR: risk ratio

1. Randomization and allocation concealment mostly unclear; and pseudo randomization in largest trial.
2. Largest trial did not restrict recruitment by recurrences per year at baseline but this was considered with risk of bias and only downgraded to moderate level of evidence.
3. Trials with 400 × 2 or 800 mg daily; similar risk in trials with < 800 mg.
4. Few participants/events and CIs include no effect and appreciable harm or benefit. One other study (1146 patients) found similar events across groups.
5. Results inconsistent among studies – considered with risk of bias and only downgraded to moderate level of evidence

DETAILS OF SIDE-EFFECTS

Study	Suppressive dose	Event	Total	Type of event	Episodic dose	Event	Total	Type of event	Result
Baker 1989	aciclovir 800 mg 1 × daily × 1 year	29	131	Not serious	aciclovir 200 mg 5 × daily × 5 days	27	130	Not serious	**RR 1.07** (0.76–1.49) 16 more per 1000 (from 56 fewer to 113 more)
Mattison 1988	aciclovir 200 mg 2 × daily × 1 year	2	47	Not serious	aciclovir 200 mg 5 × daily × 5 days	2	29	Not serious	
Sacks 1988	aciclovir 200 mg 1 × daily × 6 months	16	25	Not serious	aciclovir 200 mg 5 × daily × 5 days	14	25	Not serious	
Mattison 1988	aciclovir 200 mg 2 × daily × 1 year	0	47	Serious	aciclovir 200 mg 5 × daily × 5 days	0	29	Serious	
Mertz 1988	aciclovir 400 mg 2 × daily × 1 year	1–3%	575	Not serious	aciclovir 200 mg 5 × daily × 5 days	1–3%	571	Not serious	"similar in both groups"
Straus 1984	aciclovir 200 mg 3 × daily up to 125 days	12	17	Not serious	aciclovir 200 mg 5 × daily × 5 days	6	18	Not serious	Unclear if is number of patients
Celum 2008	aciclovir 400 mg 2 × daily × 12–18 months	75	1637	Serious – considered unrelated to study treatment	aciclovir 400 mg 3 × daily × 5 days	63	1840	Serious – considered unrelated to study treatment	**RR 1.19** (0.86–1.66) 7 more per 1000 (from 5 fewer to 25 more)
Mostow 1988	aciclovir 800 mg 1 × daily × 2 years	0	22	Serious	aciclovir 200 mg 5 × daily × 5 days	0	24	Serious	
Mostow 1988	aciclovir 800 mg 1 × daily × 2 years	20	22	Not serious	aciclovir 200 mg 5 × daily × 5 days	27	24	Not serious	Number of episodes not patients

SUPPRESSIVE VALACICLOVIR VERSUS EPISODIC VALACICLOVIR

	Suppressive	Episodic
Fife 2006	Valaciclovir 1 g × 60 days	Valaciclovir 500 mg 2 × daily × 3 days
Fife 2007	Valaciclovir 500 mg daily × 1 year	Valaciclovir 500 mg 2 × daily × 5 days
Corey 2004	Valaciclovir 500 mg daily × 8 months	Valaciclovir 500 mg 2 × daily × 5 days
Fife 2008	Valaciclovir 1 g 1 × daily × 24 weeks	Valacylovir 500 mg 2 × daily × 3 days
Patel 1997	Valaciclovir 500 mg 1 × daily × 16 weeks	Valaciclovir 500 mg 2 × daily × 5 days
Reitano 1998	Valaciclovir 250 mg, 500 mg, or 1 g once daily, or 250 mg 2 × daily × 1 year	Valaciclovir (episodic) × 5 days
Sekhin 2004	Valaciclovir 500 mg 1 × daily × 8 months	Valaciclovir 500 mg 2 × daily × 5 days

Quality assessment							No. of patients	Effect			Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Suppressive antiviral	Episodic antiviral	Relative (95% CI)	Absolute (95% CI)		
Time to first recurrent episode												
4	Randomized trials	Not serious[1]	Not serious	Not serious	Not serious	None	In 2 studies (229 patients), mean and median times were > 60 days or 185 days, compared to episodic at 32–46 days. Two other studies reported HR 0.3 (0.26–0.35) in 1484 patients and 0.35 (0.24–0.50) in 383 patients, meaning 200/1000 fewer people had a recurrence at 40 days with suppressive therapy.				⨁⨁⨁⨁ HIGH	CRITICAL
Mean number of recurrence/month												
3	Randomized trials	Not serious	Serious[2]	Not serious	Not serious	None	1037	908	–	MD **0.44 recurrences lower** (0.55 lower to 0.34 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							No. of patients	Effect			Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Suppressive antiviral	Episodic antiviral	Relative (95% CI)	Absolute (95% CI)		
Number of participants with at least on clinical recurrence												
7	Randomized trials	Not serious	Serious[3]	Not serious	Not serious	None	1096/2535 (43.2%)	922/1199 (76.9%)	**RR 0.52** (0.49–0.55)	369 fewer per 1000 (from 346 fewer to 392 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (days with pain)												
1	Randomized trials	Serious[4]	Not serious	Not serious	Very serious[5]	None	40	40	–	MD **5.4 days lower** (7.88 lower to 2.92 lower)	⨁◯◯◯ VERY LOW	CRITICAL
HSV-2 transmission to partner												
1	Randomized trials	Serious[6]	Not serious	Not serious	Serious[5]	None	14/743 (1.9%)	27/741 (3.6%)[7]	**HR 0.52** (0.27–0.99)	17 fewer per 1000 (from 0–26 fewer)	⨁⨁◯◯ LOW	IMPORTANT
								4.5%[7]		21 fewer per 1000 (from 0–33 fewer)		
Quality of life												
1	Randomized trials	Serious[4]	Not serious	Not serious	Serious[5]	None	Quality of life improved from baseline for both treatment arms (80 patients total). Improvement was slightly more with suppressive therapy but these differences were reported as not "statistically significant".				⨁⨁◯◯ LOW	CRITICAL

Quality assessment							No. of patients	Effect			Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Suppressive antiviral	Episodic antiviral	Relative (95% CI)	Absolute (95% CI)		
Compliance												
4	Randomized trials	Not serious[1]	Not serious	Not serious	Serious[8]	None	Most studies provided a placebo or drug as a suppressive regimen. In 1 study, 70% reported taking at least 95% of the prescribed doses. In another study (152 patients), 82–93% were 80% compliant or more; and in another (384 patients), 80% took over 80% of the medication. One study compared suppressive to true episodic therapy (80 patients), average intake of medication was similar (~90%).				⨁⨁⨁◯ MODERATE	CRITICAL
Side-effects (serious – not related to drug) – see also detailed table below												
4	Randomized trials	Serious[4,6]	Not serious	Not serious	Not serious	None	2364 patients received suppressive therapy and 1097 received episodic. There was 1 serious side-effect with suppressive but not related to the drug.				⨁⨁⨁◯ MODERATE	IMPORTANT
Side-effects (not serious) – see also detailed table below												
5	Randomized trials	Serious[4,6]	Not serious	Not serious	Not serious	None	123/170 (72.4%)	244/364 (67.0%)	**RR 1.06** (0.95–1.20)	40 more per 1000 (from 34 fewer to 134 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
HSV-2 shedding (assessed with: days)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	124/148 (83.8%)	81/92 (88.0%)	**RR 0.85** (0.75–0.96)	126 fewer per 1000 (from 34–209 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; HR: hazard ratio; RR: risk ratio

1. Unclear randomization and blinding but not serious to downgrade evidence
2. Unclear randomization and loss to follow-up in largest study and some unexplained heterogeneity
3. Unclear randomization and loss to follow-up in studies, and high heterogeneity that could not be explained but point estimates between RR 0.2–0.6
4. Participants were not blinded
5. Few events or few participants
6. Randomization and allocation concealment mostly unclear; and pseudo randomization in largest trial – considered often with other criteria and not downgraded.
7. Risk at 240 days (duration of trial)
8. Little data for compliance to episodic treatment

DETAILS OF SIDE-EFFECTS

Study	Suppressive dose	Event	Total	Episodic dose	Event	Total	Type of event	Result
Fife 2006	valaciclovir 1 g 1 × daily × 60 days	59	109	valaciclovir 500 mg 2 × daily × 3 days	25	42	Not serious	
Corey 2004	valaciclovir 500 mg 1 × daily × 8 months	"similar" across groups	743	valaciclovir 500 mg 2 × daily × 5 days	"similar" across groups	741	Not serious	Similar across groups
Corey 2004	valaciclovir 500 mg 1 × daily × 8 months	0	743	valaciclovir 500 mg 2 × daily × 5 days	0	741	Serious – "considered not related to drug"	
Fife 2008	valaciclovir 1 g 1 × daily × 24 weeks	185	255	valaciclovir 500 mg 2 × daily × 3 days	98	128	Not serious	Similar across groups
Fife 2008	valaciclovir 1 g 1 × daily × 24 weeks	0	255	valaciclovir 500 mg 2 × daily × 3 days	0	128	Serious – "considered not related to drug"	
Patel 1997	valaciclovir 500 mg 1 × daily × 16 weeks	adverse rate patient per day was 0.02	288	valaciclovir 500 mg 2 × daily × 5 days	adverse rate patient per day was 0.03	94	Not serious	Similar across groups
Patel 1997	valaciclovir 500 mg 1 × daily × 16 weeks	1	288	valaciclovir 500 mg 2 × daily × 5 days	0	94	Serious	Similar across groups
Reitano 1998	valaciclovir 250 mg, 500 mg, or 1 g × 1 daily, or 250 mg 1 × daily × 1 year	Not reported per patient	1078	valaciclovir × 5 days	Not reported per patient	134	Not serious	Similar across groups
Reitano 1998	valaciclovir 250 mg, 500 mg, or 1 g × 1 daily, or 250 mg 2 × daily × 1 year		1078	valaciclovir × 5 days		134	Serious – 48 patients across all groups; 1 death not related to drug	Similar across groups

SUPPRESSIVE FAMCICLOVIR VERSUS EPISODIC FAMCICLOVIR

	Suppressive	Episodic
Bartlett 2008	Famciclovir 250 mg 2 × daily × 6 months	Famciclovir 125 mg 2 × daily × 5 days

Quality assessment							No. of patients	Effect			Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Suppressive antiviral	Episodic antiviral	Relative (95% CI)	Absolute (95% CI)		
Time to first clinical recurrent episode												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[1]	None	157	155[4] 25.0%[4]	**HR 6.30** (3.90–10.17)	587 more per 1000 (from 424–696 more)	⨁⨁◯◯ LOW	CRITICAL
Mean number of recurrence/month – not measured												
Number of participants with at least 1 clinical recurrence in 6 months follow-up												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[1]	None	28/157 (17.8%)	94/155 (60.6%)	**RR 0.29** (0.21–0.42)	431 fewer per 1000 (from 352–479 fewer)	⨁⨁◯◯ LOW	CRITICAL
HSV-2 duration of shedding – not measured												
HSV-2 severity/pain – not measured												
Quality of life (Scale from: 0 to 60, optimal)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious	None	143	134	–	MD **2.02 lower** (5.14 lower to 1.09 higher)	⨁⨁◯◯ LOW	CRITICAL
Compliance – not measured2												
Side-effects (not serious)												
1	Randomized trials	Serious[1]	Not serious	Not serious[3]	Serious[1]	None	60/157 (38.2%)	50/155 (32.3%)	**RR 1.18** (0.88–1.60)	58 more per 1000 (from 39 fewer to 194 more)3	⨁⨁◯◯ LOW	IMPORTANT
HSV-2 transmission – not measured												

CI: confidence interval; HR: hazard ratio; RR: relative risk

1. Participants were not blinded, high loss to follow-up and few events or few participants
2. Study reported that 70% of people with episodic and 80% with suppressive were somewhat-to-very satisfied with treatment, and would recommend the treatment to others (no statistically significant differences)
3. Side-effects: authors reported 94% of events not related to drugs
4. Risk at 40 days of treatment.

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COMPARISON OF SIMILAR DRUGS FOR SUPPRESSIVE THERAPY AT DIFFERENT DOSAGES

Suppressive aciclovir versus suppressive aciclovir

	Suppressive	Suppressive
Douglas 1984	aciclovir 200 mg 2 × daily	aciclovir 200 mg 5 × daily

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aciclovir 200 mg 1 × daily	Aciclovir 200 mg 5 × daily	Relative (95% CI)	Absolute (95% CI)		
Time to first recurrent episode												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	Median number of days was 120 in both groups				⨁⨁◯◯ LOW	CRITICAL
Number of episodes/month												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	Mean in 2 × daily was 0.14 days (+/– 0.25) and in 5 × daily was 0.13 (+/– 0.27)				⨁⨁◯◯ LOW	CRITICAL
Number of participants with at least one clinical recurrence (follow-up: 4 months)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	19/52 (36.5%)	19/51 (37.3%)	**RR 1.02** (0.62–1.69)	**7 more per 1000** (from 142 fewer to 257 more)	⨁⨁◯◯ LOW	CRITICAL
HSV-2 severity/pain – not measured												
HSV-2 quality of life – not measured												
HSV-2 duration of shedding – not measured												
Compliance												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	Mean number of pills missed and ratio of pills missed to pills prescribed were "similar" across 2 × and 5 × daily regimens.				⨁⨁◯◯ LOW	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aciclovir 200 mg 1 × daily	Aciclovir 200 mg 5 × daily	Relative (95% CI)	Absolute (95% CI)		
Side-effects – any												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	1 patient taking ACV 5 × daily discontinued due to side-effects. Gastrointestinal effects, headache, fever, laboratory values, etc., were similar between groups.				⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; RR: risk ratio;

1. Randomization and loss to follow-up not done or unclear
2. Number of participants too low
3. Few events across studies and some inconsistency.
4. Results reported for 1 study and similar to the other study.
5. Study participants were not blinded to the treatment

SUPPRESSIVE VALACICLOVIR VERSES SUPPRESSIVE VALACICLOVIR

	Suppressive	Suppressive	Suppressive	Suppressive
Reitano 1998	valaciclovir 250 mg x 1 daily	valaciclovir 250 mg x 2 daily	valaciclovir 500 mg x 1 daily	valaciclovir 1 g x 1 daily
Johnston 2012 study 3 (assessed whether higher doses of antiviral drugs or changes in the dosing schedule could provide more potent suppression of short shedding episodes.)	valaciclovir 500 mg x 1 daily	valaciclovir 1–3 g daily		

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Valaciclovir 500 mg daily	Valaciclovir 1 to 3 g daily	Relative (95% CI)	Absolute (95% CI)		
Episode duration (assessed with: hours)												
1	Randomized trials	Serious[5]	Not serious	Not serious	Very serious[2]	None	43	43	–	median **0** (10 to 7 more)	⨁◯◯◯ VERY LOW	CRITICAL
HSV-2 shedding annualised episode rate												
1	Randomized trials	Serious[5]	Not serious	Not serious	Very serious[2]	None	43	43	–	Comparison **0 14.9 - 16.5** (14.9–16.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Number of participants with at least one clinical recurrence												
1	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	none	373/540 (69.1%)	178/269 (66.2%)	**RR 1.04** (0.94–1.16)	26 more per 1000 (from 40 fewer to 106 more)	⨁⨁⨁◯ MODERATE	CRITICAL
HSV-2 duration of shedding – not measured												
HSV-2 severity/pain – not measured												
HSV-2 quality of life – not measured												
Compliance – not measured												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Valaciclovir 500 mg daily	Valaciclovir 1 to 3 g daily	Relative (95% CI)	Absolute (95% CI)		
Side-effects – serious												
2	Observational studies	Serious[1]	Not serious	Not serious	Not serious	None	No serious adverse events reported. Single arm from another study reported no adverse events with 500 mg 1 × daily.				⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; RR: relative risk

1. Randomization and loss to follow-up not done or unclear
2. Number of participants too low
3. Few events across studies and some inconsistency.
4. Results reported for 1 study and similar to the other study.
5. Study participants were not blinded to the treatment

SUPPRESSIVE FAMCICLOVIR VERSES SUPPRESSIVE FAMCICLOVIR

	Suppressive	Suppressive	Suppressive	Suppressive	Suppressive
Diaz-Mitoma 1998	famciclovir 125 mg x 3 daily	famciclovir 250 mg x 2 daily	famciclovir 250 mg x 3 daily		
Mertz 1997	famciclovir 125 mg x 1 daily	famciclovir 125 mg x 2 daily	famciclovir 250 mg x 1 daily	famciclovir 250 mg x 2 daily	famciclovir 500 mg x 1 daily
Sacks 2004	famciclovir 125 mg x 3 daily	famciclovir 250 mg x 3 daily			

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Famciclovir ≤ 250 mg 2/ day**	**Famciclovir > 250 mg 2/ day**	**Relative (95% CI)**	**Absolute (95% CI)**		
Time to first recurrent episode (median) (follow-up: range 4–12 months)												
3	Randomized trials	Serious[1]	Not serious	Not serious	Not serious	None	Time was not consistently shorter with < 250 mg 2 × daily and not consistently longer with > 250 mg. Authors reported "similar" time (see additional tables).				⨁⨁⨁◯ MODERATE	CRITICAL
Number of episodes/month (follow-up: range 4–12 months)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	0.08 mean episodes/month with 250 mg 2 × daily but 0.15 with 500 mg 1 × daily; consistently more episodes (0.16–0.23) with < 250 mg.				⨁⨁◯◯ LOW	CRITICAL
Number of participants with at least one clinical recurrence (follow-up: range 4–12 months)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[3]	None	131/417 (24.0%)	39/142 (35.7%)	**RR 0.92** (0.58–1.45)	**25 fewer per 1000** (from 132 fewer to 141 more)	⨁⨁◯◯ LOW	CRITICAL
HSV-2 duration of shedding (positive viral cultures – asymptomatic or symptomatic swabs)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	Time to the first HSV-positive culture (HR 1.5; 95% CI, 0.9–2.6) in favour of greater dose. But 54% had shedding with greater dose versus 40% with smaller dose after 120 days.				⨁⨁◯◯ LOW	CRITICAL
HSV-2 severity/pain – not measured												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Famciclovir ≤ 250 mg 2/ day	Famciclovir > 250 mg 2/ day	Relative (95% CI)	Absolute (95% CI)		
HSV-2 quality of life – not measured												
Compliance												
2	Randomized trials	serious[1]	not serious	not serious	serious[2]	none	2 studies report from 92% to 98% of patients taking more than 80% of medication across all dosages				⨁⨁◯◯ LOW	IMPORTANT
Side-effects - non-serious and serious (follow-up: range 4 to 12 months)												
2	Randomized trials	Not serious	Not serious[4]	Not serious	Serious[3,2]	None	75/117 (64.1%)	67/112 (59.8%)	**RR 1.07** (0.87–1.31)	**42 more per 1000** (from 78 fewer to 185 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

1. Randomization and loss to follow-up not done or unclear
2. Number of participants too low
3. Few events across studies and some inconsistency.
4. Results reported for 1 study and similar to the other study.
5. Study participants were not blinded to the treatment

SUPPRESSIVE VALACICLOVIR VERSUS SUPPRESSIVE ACICLOVIR

	Suppressive	Suppressive
Johnston 2012 study 2	valaciclovir standard dose 500 mg 1 x daily	aciclovir high dose 800 mg 3 x daily
Reitano 1998	valaciclovir 250 mg, 500 mg, or 1 g 1 x daily or 250 mg 2 x daily	aciclovir 400 mg 2 x daily

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Suppressive valaciclovir	Suppressive aciclovir	Relative (95% CI)	Absolute (95% CI)		
Episode duration (assessed with: hours)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Very serious[2]	None	27	27	–	median **0 hours**	⨁◯◯◯ VERY LOW	CRITICAL
HSV-2 shedding annualised episode rate												
1	Randomized trials	Serious[1]	Not serious	Not serious	Very serious[2]	None	27	27	–	22.6–20.2 more	⨁◯◯◯ VERY LOW	IMPORTANT
Number of participants with at least 1 clinical recurrence												
1	Randomized trials	Serious[3]	Not serious	Not serious	Not serious	None	581/1078 (53.9%)	124/267 (46.4%)	**RR 1.16** (1.01–1.34)	74 more per 1000 (from 5–158 more)	⨁⨁⨁◯ MODERATE	CRITICAL
HSV-2 severity/pain – not measured												
HSV-2 quality of life – not measured												
HSV-2 duration of shedding – not measured												
Compliance (follow-up: range 4–7 weeks)												
1	Randomized trials	Serious[3]	Not serious	Not serious	Serious	None	78–96% of participants reported > 85% adherence				⨁⨁⨁◯ MODERATE	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Suppressive valaciclovir	Suppressive aciclovir	Relative (95% CI)	Absolute (95% CI)		
Side-effects – serious (follow-up: 12 months)												
2	Randomized trials	Serious[3]	Not serious	Not serious	Serious	None	1 study reported no serious adverse events; another study single arm with valaciclovir reported grade 2 neutropenia				⨁⨁⨁◯ MODERATE	IMPORTANT

CI: confidence interval; MD: mean difference; RR: relative risk

1. Participants were not blinded to the study treatment
2. Few events or participants
3. Randomization was unclear, and incomplete outcome assessment.

SUPPRESSIVE FAMCICLOVIR VERSUS SUPPRESSIVE VALACICLOVIR

	Suppressive	Suppressive
Wald 2006 Study 1 (the effect of the treatments on suppression of clinical genital herpes recurrences.)	famciclovir 250 mg 2 ´ daily	valaciclovir 500 mg 1 ´ daily
Wald 2006 Study 2 (the effect of the treatments on HSV shedding from the genital area.)	famciclovir 250 mg 2 ´ daily	valaciclovir 500 mg 1 ´ daily

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Famciclovir 250 mg ´2/day	Valaciclovir 500 mg ´1/day	Relative (95% CI)	Absolute (95% CI)		
Time to first clinical recurrence												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	Time to first clinical recurrence of genital herpes was similar in both groups, HR 1.17 (95% CI: 0.78 –1.76) for famciclovir compared with valaciclovir				⨁⨁◯◯ LOW	CRITICAL
Mean number of recurrences over the study period												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	0.11 with famciclovir versus 0.10 with valaciclovir (P = 0.39)				⨁⨁◯◯ LOW	CRITICAL
Number of participants with at least one clinical recurrence												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	55/159 (34.6%)	47/161 (29.2%)	**RR 1.18** (0.86–1.63)	63 more per 1000 (from 49 fewer to 220 more)	⨁⨁◯◯ LOW	CRITICAL
HSV-2 severity/pain – not measured												
HSV-2 quality of life – not measured												
HSV-2 shedding (assessed with: days HSV detected – asymptomatic and symptomatic)												
1	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]		3.2% of days with famciclovir (n=34) and 1.3% with valaciclovir (n=36) – RR 2.23 (1.18–4.89) in favour of valaciclovir				⨁⨁◯◯ LOW	CRITICAL
Compliance												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	Median adherence ranged from 97–100% in both groups				⨁⨁◯◯ LOW	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Famciclovir 250 mg ´2/day	Valaciclovir 500 mg ´1/day	Relative (95% CI)	Absolute (95% CI)		
Side-effects – not serious (follow-up: range 10–16 weeks)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	27/193 (14.0%)	29/197 (14.7%)	**RR 0.95** (0.59–1.54)	7 fewer per 1000 (from 57 fewer to 76 more)	⨁⨁◯◯ LOW	IMPORTANT
Side-effects – serious – not related to drug (follow-up: range 10–16 weeks)												
2	Randomized trials	Serious[1]	Not serious	Not serious	Serious[2]	None	0/193 (0%)	3/197 (1.5%)	**RR 0.26** (0.03–2.35)	11 fewer per 1000 (from 15 fewer to 21 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: risk ratio

1. Randomization and loss to follow-up unclear, unclear assessment of side-effects.

2. Few participants or events.

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SUPPRESSIVE THERAPY FOR PEOPLE LIVING WITH HIV

Efficacy of different suppressive drugs versus no treatment for people living with HIV											
Quality assessment							Summary of findings				
No. of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Suppressive		Risk with placebo	Risk difference with Suppressive therapy
Aciclovir 400 mg 2 × daily vs placebo: HIV/HSV-2 transmission and acquisition											
8354 (3 RCTs)	Not serious	Not serious	Not serious	Serious[1]	None	⨁⨁⨁◯ MODERATE	92/4179 (2.2%)	115/4175 (2.8%)	**RR 1.26** (0.96–1.64)	**Moderate**	
										31 per 1000	**8 more per 1000** (1 fewer to 20 more)
Aciclovir 400 mg 2 × daily vs placebo: HIV viral load											
1579 (2 RCTs)	Not serious	Not serious	Not serious	Serious[1]	None	⨁⨁⨁◯ MODERATE	416/721 (57.7%)	518/858 (60.4%)	**RR 1.04** (0.96–1.13)	**Moderate**	
										533 per 1000	**21 more per 1000** (21 fewer to 69 more)
Aciclovir 400 mg 2 × daily vs placebo: incidence of genital ulcers											
6972 (3 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ HIGH	1227/3488 (35.2%)	468/3484 (13.4%)	**RR 0.38** (0.35–0.42)	**Moderate**	
										328 per 1000	**203 fewer per 1000** (213 fewer to 190 fewer)
Aciclovir 400 mg 2 × daily vs placebo: side-effects											
4994 (2 RCTs)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	63/2502 (2.5%)	75/2492 (3.0%)	**RR 1.20** (0.86–1.66)	**Moderate**	
										20 per 1000	**4 more per 1000** (3 fewer to 13 more)
Aciclovir 800 mg 2 × daily for 1 month vs placebo: percentage of times of HIV cervical shedding											
128 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	53/66 (80.3%)	40/62 (64.5%)	**RR 0.80** (0.64–1.00)	**Moderate**	
										803 per 1000	**161 fewer per 1000** (289 fewer to 0 fewer)

Efficacy of different suppressive drugs versus no treatment for people living with HIV											
Quality assessment							**Summary of findings**				
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Suppressive**		**Risk with placebo**	**Risk difference with Suppressive therapy**
Aciclovir 800 mg 2 × daily for 1 month vs placebo: the mean plasma concentration of HIV-1											
128+60 (2 RCTs)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	One study reported that HIV-1 log10 copies/mL, plasma in **placebo**: mean 4.26 (4.07–4.44) **in aciclovir: mean** 3.78 (3.50–4.05). Another study reported that: aciclovir versus control: plasma HIV-1 RNA detection OR 1.93; 95% CI: 0.66–5.68 (*P* = 0.23).				
Valaciclovir 500 mg 2 × daily for 6 months vs placebo: no recurrent clinical episodes											
293 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	26/99 (26.3%)	126/194 (64.9%)	**RR 2.47** (1.75–3.49)	**Moderate**	
										263 per 1000	**386 more per 1000** (197 more to 654 more)
Valaciclovir 500 mg 2 × daily vs placebo for 6 months: side-effects											
293 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	57/99 (57.6%)	145/194 (74.7%)	**RR 1.30** (1.08–1.57)	**Moderate**	
										576 per 1000	**173 more per 1000** (46 more to 328 more)
Valaciclovir 500 mg 2 × daily vs placebo for 3 months: impact on plasma HIV-1 RNA/genital HIV-1 RNA detected											
196 (2 RCTs)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	68/98 (69.4%)	55/98 (56.1%)	**RR 0.74** (0.39–1.37)	694 per 1000	**180 fewer per 1000** (423 fewer to 257 more)
Famciclovir 500 mg 2 × daily vs placebo: no lesion present											
48 (1 RCT)	Not serious	Not serious	Not serious	Very serious[1]	None	⨁⨁◯◯ LOW	5/24 (20.8%)	0/24 (0.0%)	**RR 0.09** (0.01 to 1.56)	**Moderate**	
										208 per 1000	**190 fewer per 1000** (206 fewer to 117 more)

CI: Confidence interval; RCT: randomized control trial; RR: risk ratio

1. Imprecise results due to wide CI and/or few events/sample size

Efficacy of different suppressive drugs for HIV patients											
Quality assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With aciclovir	With valaciclovir		Risk with aciclovir	Risk difference with valaciclovir
Valaciclovir 500 mg 2 × daily vs aciclovir 400 mg 2 × daily: number of people healed (ulcer healing)											
704 (1 RCT)	Not serious	Not serious	Not serious	Serious[1]	None	⨁⨁⨁◯ MODERATE	272/349 (77.9%)	291/355 (82.0%)	**RR 1.05** (0.98–1.13)	779 per 1000	**39 more per 1000** (16 fewer to 101 more)
Valaciclovir 1000 mg 1 × daily vs aciclovir 400 mg 2 × daily: number of people healed (ulcer healing)											
707 (1 RCT)	Not serious	Not serious	Not serious	Serious[1]	None	⨁⨁⨁◯ MODERATE	272/349 (77.9%)	254/358 (70.9%)	**RR 0.91** (0.83–0.99)	779 per 1000	**70 fewer per 1000** (132 fewer to 8 fewer)
Valaciclovir 500 mg 2 × daily vs aciclovir 400 mg 2 × daily: side-effects											
704 (1 RCT)	Not serious	Not serious	Not serious	Serious[1]	None	⨁⨁⨁◯ MODERATE	267/349 (76.5%)	268/355 (75.5%)	**RR 0.99** (0.91–1.07)	765 per 1000	**8 fewer per 1000** (69 fewer to 54 more)
Valaciclovir 1000 mg once daily vs aciclovir 400 mg twice daily: side-effects											
707 (1 RCT)	Not serious	Not serious	Not serious	Serious[1]	None	⨁⨁⨁◯ MODERATE	267/349 (76.5%)	284/358 (79.3%)	**RR 1.04** (0.96–1.12)	765 per 1000	**31 more per 1000** (31 fewer to 92 more)

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. Imprecise results due to wide CIs and/or few events/sample size

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