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[Intervention Review]

Interventions for men and women with their first episode of genital herpes

Rachel Heslop[1], Helen Roberts[1], Deralie Flower[1], Vanessa Jordan[1]

[1]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand

Contact address: Rachel Heslop, Department of Obstetrics and Gynaecology, University of Auckland, Private Bag 92019, Auckland, 1023, New Zealand. rhes003@aucklanduni.ac.nz, heslop.rachel@gmail.com.

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ABSTRACT

Background

Genital herpes is incurable, and is caused by the herpes simplex virus (HSV). First-episode genital herpes is the first clinical presentation of herpes that a person experiences. Current treatment is based around viral suppression in order to decrease the length and severity of the episode.

Objectives

To determine the effectiveness and safety of the different existing treatments for first-episode genital herpes on the duration of symptoms and time to recurrence.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (from inception to April 2016), MEDLINE (from inception to April 2016), the Specialised Register of the Cochrane Sexually Transmitted Infections Review Group (from inception to April 2016), EMBASE (from inception to April 2016), PsycINFO (from inception to April 2016), CINAHL (from inception to April 2016), LILACS (from inception to April 2016), AMED (from inception to April 2016), and the Alternative Medicines Specialised Register (from inception to April 2016). We handsearched a number of relevant journals, searched reference lists of all included studies, databases of ongoing trials, and other Internet databases.

Selection criteria

We included randomised controlled trials (RCTs) on participants with first-episode genital herpes. We excluded vaccination trials, and trials in which the primary objective assessed a complication of HSV infection.

Data collection and analysis

All studies written in English were independently assessed by at least two review authors for inclusion, risk of bias for each trial, and to extract data. Studies requiring translation were assessed for inclusion, trial quality, and data extraction by external translators.

Main results

We included 26 trials with 2084 participants analysed. Most of the studies were conducted in the United Kingdom (UK) and United States (US), and involved men and women experiencing their first episode of genital herpes, with the exception of three studies which included only women. We rated the majority of these studies as having an unclear risk of bias; largely due to lack of information supplied in the publications, and due to the age of the trials. This review found low quality evidence from two studies of oral acyclovir, when compared to placebo, reduced the duration of symptoms in individuals undergoing their first episode of genital herpes (mean difference (MD) -3.22,

95% confidence interval (CI) -5.91 to -0.54; I^2 = 52%). In two studies (112 participants), intravenous acyclovir decreased the median number of days that patients with first-episode herpes suffered symptoms. Oral valaciclovir (converted to acyclovir) also showed a similar length of symptom duration when compared to acyclovir in two studies.
There is currently no evidence that topical acyclovir reduces symptoms (MD -0.61 days, 95% CI -2.16 to 0.95; 3 RCTs, 195 participants, I^2 statistic = 56%). There is also no current evidence that the topical treatments of cicloxolone cream, carbenoxolone sodium cream, adenosine arabinoside, idoxuridine in dimethyl sulfoxide, when compared to placebo reduced the duration of symptoms in people undergoing their first episode of herpes.

Two studies reported no evidence of a reduction in the number of median days to recurrence following treatment with oral acyclovir versus placebo. Adverse events were generally poorly reported by all of the included studies and we were unable to quantitatively analyse this outcome. For those taking acyclovir, there were no serious adverse events; the most common adverse events reported for oral acyclovir were coryza, dizziness, tiredness, diarrhoea and renal colic. For intravenous acyclovir these were phlebitis, nausea and abnormal liver function tests and for topical acyclovir there was pain with the topical application.Those undergoing interferon treatment had significantly more adverse events compared to those taking placebo.

Authors' conclusions

There is low quality evidence from this review that oral acyclovir reduced the duration of symptoms for genital herpes. However, there is low quality evidence which did not show that topical antivirals reduced symptom duration for patients undergoing their first episode of genital herpes. This review was limited by the inclusion of skewed data, resulting in few trials that we were able to meta-analyse.

PLAIN LANGUAGE SUMMARY

Treatment for the first time men and women get genital herpes (first-episode genital herpes)

Review question
The aim of this research was to look at the positive and adverse effects of treatments, on the duration of symptoms, in people who have their first episode of genital herpes.

Background
Genital herpes is caused by the herpes simplex virus (HSV) that is primarily sexually transmitted (skin-to-skin contact). First-episode genital herpes is the first time a person experiences the symptoms of genital herpes. The main feature of genital herpes are painful skin lesions. Treatment is based around viral suppression in order to decrease the length and severity of the symptoms.

Study characteristics
We included 26 randomised controlled trials (RCTs) trials with 2084 participants that looked at treatments for first-episode genital herpes versus placebo or another treatment. The trials all included people who were having their first episode of genital herpes and were conducted in various countries around the world. Three of the trials included only women, and in all the trials the participants had had symptoms for eight days or less. Fifteen of the 26 trials were funded by a pharmaceutical company.

Key results
The evidence is current to April 2016. The evidence shows that oral and intravenous acyclovir may be effective in reducing the number of days of symptoms in someone with first-episode genital herpes. Oral valaciclovir showed a similar length of symptom duration as acyclovir. We did not find enough evidence to support the use of topical treatments. There was also no evidence that any of the treatments reduced the time between episodes for people with genital herpes. The evidence presented here is mostly of low quality. The studies included were mainly conducted in the 1980s and at this time the brief way studies were reported does not allow us to adequately judge the quality of the included studies.

Quality of the evidence
The evidence provided by this review is of low quality. Although there are 26 included studies, the meta-analyses created in this review at the most, had three included studies. This was mainly due to the low number of studies that looked at each different type of antiviral. It was also unclear as to how well the included studies were conducted, as the methods for each of the individual studies did not report enough detail to judge each study's quality, inconsistence and this also affected the overall quality of the review.

Summary of findings for the main comparison. Oral acyclovir versus placebo for men and women with their first episode of genital herpes

Oral acyclovir versus placebo for men and women with their first episode of genital herpes

Patient or population: men and women with their first episode of genital herpes
Setting: STD and family planning clinics
Intervention: oral acyclovir
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral acyclovir				
Duration of symptoms from onset of treatment	The mean duration of symptoms from onset of treatment in the intervention group was 3.22 days fewer than that with placebo (5.91 fewer to 0.54 fewer)	-	82 (2 RCTs)	⊕⊕⊖⊖ **Low[1, 2]**	
Adverse events	Study population Not pooled	Not pooled	130 (2 RCTs)	⊕⊖⊖⊖ **Very low[2, 3,5]**	There were no severe adverse events. Adverse events were unable to be pooled as they were only reported in two studies and were not reported in a consistent way. Adverse events recorded for those taking this medication included coryza, dizziness, tiredness, diarrhoea and renal colic
Duration of lesions from onset of treatment	The mean duration of lesions from onset of treatment in the intervention group was 3.51 fewer days than that with placebo (6.19 fewer to 0.82 fewer)	-	86 (2 RCTs)	⊕⊕⊖⊖ **Low[1, 2]**	
Time to recurrence	Data were not analysed using the correct method but statistical analysis did not show any difference in median time to recurrence in the two groups	Not pooled	198 (2 RCTs)	⊕⊖⊖⊖ **Very low[2,4]**	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 for risk of bias. There was unclear risk in both studies for randomisation and allocation concealment. Only one study used blinding and one study was graded high risk for attrition and reporting biases.
[2] Downgraded by 1 for imprecision. There were very low sample numbers in these two studies.
[3] Downgraded by 1 for risk of bias. Studies reporting adverse events were rated as unclear for the majority of the risk of bias items.
[4] Downgraded by 2 for risk of bias as both studies were unclear for allocation concealment and randomisation and there is the potential for a substantial effect due to dropouts as actual numbers followed up were not reported
[5] Downgraded by 1 for imprecision based on very wide confidence intervals

Summary of findings 2. Topical acyclovir versus placebo for men and women with their first episode of genital herpes

Topical acyclovir versus placebo for men and women with their first episode of genital herpes

Patient or population: men and women with their first episode of genital herpes
Setting: STD and family planning clinics
Intervention: topical acyclovir
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with topical acyclovir				
Duration of symptoms from onset of treatment		The mean duration of symptoms from onset of treatment in the intervention group was 0.61 days fewer than that with placebo (2.16 fewer to 0.95 more)	-	195 (3 RCTs)	⊕⊕⊖⊖ **Low[1, 2]**	One included study had given all subjects oral acyclovir
Duration of lesions from onset of treatment		The mean duration of lesions from onset of treatment in the intervention group was 0.86 days fewer than that with placebo (2.15 fewer to 0.42 more)	-	195 (3 RCTs)	⊕⊕⊖⊖ **Low[1, 3]**	One included study had given all subjects oral acyclovir
Adverse events - pain with topical application	Study population	Study population	RR 0.74 (0.46 to 1.20)	247 (3 RCTs)	⊕⊕⊖⊖ **Low[1,5]**	
	242 per 1000	179 per 1000				

		(111 to 290)				
	Moderate	Moderate				
	235 per 1000	174 per 1000 (108 to 282)				
Time to recurrence	Data were not pooled. Time to reccurrence ranged from 70-116 days	Data were not pooled. Time to recurrence ranged from 70-116 days	The were no differences reported between the two groups	129 (3 RCTs)	⊕⊖⊖⊖ **Very low[1,4]**	Data were not analysed using the correct method. Medians were presented

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 for risk of bias. All trials had unclear risk of bias for randomisation and allocation concealment.
[2] Downgraded by 1 for inconsistency. Heterogeneity was 56%.
[3] Downgraded by 1 for inconsistency. Heterogeneity was 72%.
4 Downgraded by 2 for risk of bias with regard to incomplete data not many participants were followed up.
[5] Downgraded by 1 for imprecision based on very wide confidence intervals

BACKGROUND

Description of the condition

Genital herpes is a sexually transmitted infection caused by herpes simplex virus (HSV) type 1 and 2. HSV-2 infections usually cause more recurrent and severe symptoms, and initial infections (primary infections) are generally more severe than recurrences. HSV-2 infection is more common in women, possibly because the rate of male-to-female transmission is at least twice that of female-to-male transmission (Azwa 2009). The prevalence of genital HSV infection increases with age and numbers of sexual partners, with higher rates in specific ethnic and lower socioeconomic groups (Azwa 2009). The strongest predictor for genital HSV infection is a person's number of lifetime partners (Azwa 2009). HSV infection results in lifelong infection, which can be asymptomatic or present with recurrent lesions. It is estimated that up to 70% of all genital HSV-2 is transmitted during asymptomatic shedding from an index partner with HSV-2 (Azwa 2009). The virus enters the body by direct contact of the infected person's secretions or mucus membranes with the skin or mucus membrane of another. The herpes virus multiplies in the basal epithelial layer and then becomes latent in the dorsal root ganglion where it can reactivate spontaneously and travel back to the epithelium. This is known as viral shedding (Whitley 1998).

The initial infection may or may not cause symptoms, and is followed by seroconversion with type-specific antibodies four to six weeks after infection. There are two types of symptomatic first-episode occurrences. The first is a first episode of herpes in non-primary infection which occurs in a person who was non-symptomatic when initially infected with HSV, the second is a first episode of herpes in primary infection which is when HSV causes a symptomatic episode in a HSV-seronegative person. First episode of herpes in non-primary infections which is in an already infected individual are associated with fewer systemic symptoms, a shorter duration of disease, a shorter duration of viral shedding, and fewer lesions than a first episode of herpes with a primary infection(Azwa 2009). A first episode can last up to two weeks if untreated (Cernik 2008). As symptomatic, first episode herpes with primary infection is usually more severe than a first episode of herpes with a non primary infection, it is important to ascertain that interventions are effective for these individuals experiencing a first episode of herpes with a primary infection.

After an incubation period of one to 26 days, classical primary genital herpes begins with prodromal symptoms, characterised by localised pain or tingling lasting up to 24 hours. Clinical manifestations of herpes are diverse (Corey 1983b). However, 'classic' prodromal symptoms are followed by the appearance of randomly distributed vesicles clustered on a red base. Tiny papules develop into vesicles, which subsequently ulcerate and crust. Constitutional symptoms such as fever, chills, fatigue, and muscle aches accompany the disease and last 10 to 14 days. Enlarged inguinal or femoral glands may accompany constitutional symptoms, and dysuria is common in women.

For women, the classic clinical picture is that of painful vaginal and vulva lesions (Corey 1982b). However, infection of the cervix, often subclinical, is common. Men typically develop lesions on the glans, prepuce, or shaft of the penis (Corey 1982b). Male circumcision significantly reduces the incidence of HSV-2 infection (Tobian 2009), and appears to reduce the number of recurrences and evidently prolongs the disease-free period between two recurrences (Jerath 2009). Male circumcision does not affect HSV-2 acquisition among female partners (Tobian 2012).

Extragenital complications occur in a minority of people who present with primary HSV infection. These include central nervous system disease, such as aseptic meningitis, encephalitis, or transverse myelitis; end organ disease including hepatitis or pneumonitis; and disseminated HSV (Corey 1982b).

Description of the intervention

There is no therapy or vaccine to prevent HSV, though the use of condoms offers moderate protection from acquisition (Martin 2009). The aim of treatment is to improve symptoms and time to recovery. Antiviral agents have been shown to reduce the duration and severity of symptoms, reduce healing times, and decrease the duration of viral shedding in first episode genital herpes (Azwa 2009). Which antiviral provides the best treatment and in which form (oral, topical, subcutaneous, intramuscular, or intravenous) needs to be confirmed. Treatment of symptomatic episodes of HSV does not alter the clinical course of the disease and has no effect on the rates of recurrences of genital herpes (Azwa 2009).

Currently, there are three classes of drugs licensed for the treatment of HSV symptomatic episodes, all of which target viral deoxyribonucleic acid (DNA) replication. Guanosine analogues, including acyclovir, valicyclovir, famciclovir, and ganciclovir, are the drugs of choice for the management of first episode HSV. The acyclic nucleotide analogue, cidofovir, and the pyrophosphate analogue, foscarnet, are reserved for use in resistant viruses. Acyclovir, a thymidine nucleoside analogue, was the first drug introduced to treat HSV infection. It has poor bioavailability and a short half-life and, as a result, requires frequent dosing. Valacyclovir is a prodrug of acyclovir, and famciclovir is a prodrug of the guanosine nucleoside analogue, penciclovir (Azwa 2009).

Acyclovir can be administered topically, orally, or intravenously. When administered within 72 hours of the formation of the lesions, acyclovir shortens the course of the first episode attack, prevents new lesion formation, and helps decrease any accompanying constitutional symptoms (Azwa 2009).

Adverse effects caused by Acyclovir, valacyclovir, and famciclovir are rare and include nausea, vomiting, headache, and diarrhoea (Azwa 2009). Ganciclovir (myelosuppressive), foscarnet (nephrotoxic), and cidofovir (nephrotoxic) are very toxic drugs and are not used as a first-line treatment (Vajpayee 2000).

Imidazoquinolines such as imiquimod and resiquimod have been found in preclinical studies to be immune response modifiers by inducing cytokines (Stanley 2002). Imiquimod is currently used as a topical treatment for external genital and perianal warts in adults (approved by the US Food and Drug Administration (FDA) in 1997). Application is topical, which appears to have minimal systemic absorption. Adverse reactions are mainly related to the application site with some people reporting systemic symptoms (Gupta 2002).

Interferons are well known for their antiviral effects, and are also potent cell growth regulators, and have immunomodulation properties (Katze 2002). Some randomised double-blind placebo-controlled trials have reported positive results with the use of Interferon topically. The treatment was also reported to be well tolerated and only minor local reactions were noted (Chiu 2011).

Natural products include plant extracts, antioxidants, and vitamins. Many small molecules, including phenols, polyphenols, terpenes, flavonoids, and sugar-containing compounds, have potential anti-HSV activity (Zhong 2012). Some of the products that have been trialed include *Clinacanthus nutans (C. nutans)* (Kongkaew 2011), lysine, vitamin C, zinc, vitamin E, and adenosine monophosphate (Gaby 2006). However, most of the studies were for recurrent genital herpes, so treatment of first episodes needs to be studied further.

How the intervention might work

Acyclovir, valacyclovir, and famciclovir are competitive inhibitors of viral DNA polymerase, resulting in inhibition of viral DNA synthesis. The drugs have an excellent margin of safety because they are converted by viral thymidine kinase to the active drug only inside virally infected cells (Cernik 2008).

Imiquimod and its potent analogue (100 times more), resiquimod, are from the family of imidazoquinolines. Both have mechanisms of action that modify the immune response. This is mediated through the induction of various cytokines, including tumour necrosis factor-alpha (TNF-α), interferon-alpha (IFN-α), and interleukins (IL) such as IL-1, IL-6, and IL-12 (Brown 2002). It is thought that it may stimulate or enhance the innate and adaptive immune system (Gupta 2002).

Interferon works by stimulating the host immune system by increasing activation of natural killer cells, macrophages, and cytotoxic T cells, therefore interfering with the lifecycle of the virus (Chiu 2011). Natural products contain a wide variety of compounds that have been found to have anti-HSV properties. The majority have a mechanism of action that inhibits attachment and entry of the virus into the host cell. However, the specific mechanisms and targets of most of the active natural products are unknown and still require investigation (Zhong 2012).

Why it is important to do this review

HSV is a major global health problem. It is the leading cause of encephalitis and genital ulcerative disease, and a major cofactor for HIV infection (Azwa 2009). The virus can establish latency, reactivate frequently, and be horizontally and vertically transmitted during periods of unrecognised or asymptomatic shedding. Seroprevalence varies widely between different geographical and population groups and is particularly high in HIV-infected individuals, reaching levels over 90% in countries where HIV is endemic (Malkin 2004; Weiss 2004).

Genital herpes is a significant risk factor for acquiring HIV for both men and women, which is of serious concern. Many mechanisms have been suggested as to how this takes place. It is thought to be due to the presence of broken skin giving transmission enhancement, or that HSV interacts with HIV leading to increased success of the infection (Huang 2012). One systematic review found an approximately three-fold increase in risk of HIV acquisition in men and women infected with HSV-2 (Freeman 2006).

There is significant concern surrounding maternal herpes infection due to the risk of neonatal infection, which has been shown to lead to significant morbidity and mortality (Brown 2005). The most critical determinant of neonatal infection is first episode of primary infection genital HSV infection near delivery. This clinical observation may be related to the absence of maternal anti-HSV antibodies and to greater viral exposure during first episode of primary infection herpes. Other predictors of neonatal infection include viral shedding during labour, invasive fetal monitoring and premature delivery (Brown 2003). Although cesarean section does not completely eliminate the risk for HSV transmission to the infant, women with genital herpetic lesions at the onset of labour should deliver by cesarean section to prevent neonatal HSV infection (Workowski 2010).

Treatment of the disease in the most effective and beneficial way is imperative. If HSV-2 is a cofactor for HIV infection then HSV-2 treatment may have a role as an HIV prevention strategy. This review will help to provide clarity on which is the most effective treatment regime in terms of medication, dose, and application by demonstrating a clear picture of the current evidence that exists within the literature. This will in turn help to clarify the situation for health practitioners regarding the extent of improvement of health outcomes for particular treatments, along with their adverse events.

This review addresses first-episode disease only. A separate Cochrane review addresses the use of oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients (Le Cleach 2014).

OBJECTIVES

To determine the effectiveness and safety of the different existing treatments for first-episode genital herpes on the duration of symptoms and time to recurrence.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished parallel randomised controlled trials (RCTs) and cluster-RCTs. We excluded quasi-RCTs.

Inclusions:

- drug dosing trials;
- suppressive therapy regimens (long-term therapy) for first episodes.

Exclusions:

- studies of vaccinations;
- studies for which the objective was to look at the treatment for complications of herpes simplex virus (HSV), for example, herpes simplex encephalitis or herpes proctitis.

Types of participants

Men and women, inclusive of pregnant women, with their first episode of genital herpes (including immunocompetent and immunodeficient individuals). We included studies if they included participants with first-episode disease and data were reported separately for this group.

Types of interventions

We looked at antivirals (both topical and systemic), interferon (both topical and systemic), immune modulators such as imiquimod (topical or analogue, e.g. resiquimod) and natural products which

were compared with no treatment, placebo, other medication, or differing drug dosages. The timing of the treatments is in relation to the onset of symptoms. The interventions are:

Antivirals

- antiviral (such as acyclovir: topical and systemic) versus placebo
- antiviral (topical and systemic) versus no treatment
- antiviral (topical and systemic) versus other medication

Interferon (immune modulator)

- Interferon (topical and systemic) versus placebo
- Interferon (topical and systemic) versus no treatment
- Interferon (topical and systemic) versus other medication

Imiquimod (immune modulator)

- imiquimod (topical or analogue) versus placebo
- imiquimod (topical or analogue) versus no treatment
- imiquimod (topical or analogue) versus other medication

Natural product

- natural product versus placebo
- natural product versus no treatment
- natural product versus other medication

Antiviral + natural product

- antiviral + natural product versus placebo
- antiviral + natural product versus no treatment
- antiviral + natural product versus other medication

Dosage studies

- antiviral versus antiviral (both topical or systemic)
- interferon versus interferon (both topical or systemic)
- imiquimod versus imiquimod (both topical and analogue)
- natural product versus natural product

Types of outcome measures

Primary outcomes

1. Duration of symptoms from onset of treatment: symptoms are defined by the trial authors. When several symptoms are reported, we included the longest duration.
2. Time to first recurrence.
3. Adverse events.

Secondary outcomes

4. Duration of lesions from onset of treatment: we defined this as time to complete lesion healing.
5. Neonatal effects: as defined by the trial authors.
6. Caesarean section delivery.

Search methods for identification of studies

RH and VJ identified as many relevant RCTs as possible of 'antiviral agents, interferon, imiquimod, and biological agents' for 'genital herpes', irrespective of their language of publication, publication date and publication status (published, unpublished, in press, and in progress).

Electronic searches

The Trials Search Co-ordinator (TSC) of the Cochrane Sexually Transmitted Infections Review Group (STIG) conducted a comprehensive search strategy to capture as many relevant RCTs as possible in electronic databases. We used both electronic searching in bibliographic databases and handsearching, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We downloaded and managed the search results using Endnote bibliographic software. We deleted duplicate records of the same study. See Appendix 1 for the electronic search strings.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) Ovid platform (from inception to April 2016), MEDLINE Ovid platform (from inception to April 2016), EMBASE.com (from inception to April 2016), PsycINFO EBSCOHost platform (from inception to April 2016), CINAHL EBSCOHost platform (from inception to April 2016), LILACS iAHx interface (from inception to April 2016) and AMED (from inception to April 201)

We used the Cochrane highly sensitive search strategy for identifying RCTs (sensitivity- and precision-maximising version; 2008 revision) in Ovid format in MEDLINE (Higgins 2011).

Searching other resources

We attempted to identify additional relevant RCTs by using the following methods.

1. Searching in Complementary and Alternative Medicines (CAM) Specialised Register (ProCite Database): inception to present.
2. Searching in trial registers:
   - World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP portal) (http://apps.who.int/trialsearch/): inception to present.
   - ClinicalTrials.gov (http://clinicaltrials.gov/): inception to present.
3. Searching in Web of Science (http://thomsonreuters.com/web-of-science/): inception to present.
4. Searching in Proquest Dissertations and Theses (http://search.proquest.com): inception to present.
5. Searching for grey literature in System for Information on Grey Literature in Europe 'OpenGrey' (http://www.opengrey.eu/): inception to present.
6. Searching by contacting pharmaceutical companies producing 'antiviral agents, interferon, imiquimod, and biological agents' for 'genital herpes'.

7. Handsearching conference proceedings from the following meetings:
   - International Society for Sexually Transmitted Diseases Research - ISSTDR (http://www.isstdr.org/): 2007, 2009, 2011, 2013, and 2015.
   - British Association for Sexual Health and HIV - BASHH (http://www.bashh.org/): 2004, 2006, 2007, 2009, 2013, 2014, and 2015.
   - International Congress on Infectious Diseases - ICID (http://www.isid.org/): 2010 and 2012, and 2014.
   - International Union against Sexually Transmitted Infections - IUSTI (http://www.iusti.org/): 2011 and 2012.
   - International Society for Infectious Diseases - ISID (http://www.isid.org/): 2011.
   - International Meeting on Emerging Diseases and Surveillance - IMED (http://www.isid.org/): 2007, 2009, 2011, 2013, and 2014.
   - Interscience Conference on Antimicrobial Agents and Chemotherapy - ICAAC (http://www.icaac.org/): 2011, 2012, 2013, 2014, and 2015.
   - International Federation of Gynecology and Obstetrics - FIGO (http://www.figo.org/): 2012 and 2015.
8. Handsearching within previous systematic reviews and other relevant publications on the same topic.
9. Handsearching within reference lists of all relevant RCTs identified by others methods.
10. Contacting drug companies for trials.

Data collection and analysis

Selection of studies

After all searches were conducted, we checked for duplicates using EndNote. Two review authors (RH, VJ) independently assessed trials for inclusion by scanning the titles and abstracts based on the established inclusion criteria. We then compared which trials had been identified and obtained full-text articles in order to select the final studies for possible inclusion in the review. A third review author (HR) helped resolve any disagreements regarding study inclusion. We sought additional information from the trial authors if there was insufficient information to make a decision about eligibility. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and 'Characteristics of excluded studies' table. We did not impose any language restrictions.

Data extraction and management

Three review authors (RH, DF, VJ) independently extracted data from eligible studies using a data extraction form that was developed by the review authors (Appendix 2). We resolved any differences by discussion or by consultation (or both) with a third review author (HR, VJ) to reach consensus. Extracted data included study characteristics and outcome data (see data extraction form, Appendix 2). Where there were multiple publications of one study, we used the main trial report as the reference and extracted any additional details from secondary papers. We contacted trial authors if further data was required, such as methods or results so as to confirm the suitability of the study for meta-analysis. We routinely sought information on whether data was recorded that was not reported in the published paper from the corresponding authors for all included trials.

Assessment of risk of bias in included studies

Two individuals (RH, VJ or DF) independently assessed the quality of each of the selected studies using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We classified studies as 'low risk of bias', 'high risk of bias', or 'unclear risk of bias', reporting on the following seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.

We resolved any disagreements regarding bias by consensus or discussion with a third review author (HR or VJ).

We searched for within-trial selective reporting, such as reporting of outcomes in insufficient detail or trials failing to report obvious outcomes. We sought protocols and compared the outcomes of the protocol with the outcomes in the final study.

The conclusion of all judgements is presented in the 'Risk of bias' table, which by means of sensitivity analysis, is incorporated into the interpretation of review findings.

Measures of treatment effect

We expressed dichotomous data, such as caesarean section delivery, as a risk ratio (RR) and 95% confidence intervals (CIs). We expressed continuous data, such as duration of symptoms, as a mean difference (MD) between treatment groups, with 95% CIs. If similar outcomes were reported on different scales we planned to use the standardised mean difference (SMD). We utilised the most detailed numerical data available that provided a similar way to analyse the included studies (e.g. P values, test statistics) where data required to calculate RRs or MDs were unavailable. We used hazard ratios (HRs) to express time-to-event outcomes, where data permitted (duration of symptoms, duration of lesions, time to recurrence). Many studies presented data as medians as the data were heavily skewed. These medians are presented in additional tables.

Unit of analysis issues

In the case of cross-over trials, we planned to include only the first phase data. However, we did not include any cross-over trials in this review.

In the case of cluster-randomised data, we planned to employ the interclass correlation coefficient (ICC) as discussed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the ICC was not available then we planned to borrow a suitable factor from other trials as an estimate of relative variability. We did not, however, have any cluster-randomised trials.

For adverse events where it was not clear if individuals had suffered from more than one adverse event, we did not generate a summary statistic. If we found studies with more than one intervention versus placebo or a third intervention, we planned to ensure double-counting of the participants would not have occurred by splitting the comparison group between the two interventions (Higgins 2011).

Dealing with missing data

We attempted to contact the primary trial author for further information when there were missing data. However, due to the age of the included trials, we were unable to get additional information for the majority of trials. We noted characteristics of any participants that left the study; this enabled us to determine if the groups remain balanced. We looked at the method used to impute the missing data if intention-to-treat (ITT) analyses were supplied by the primary trial authors.

When there was sufficient detail reported to calculate the MDs but no information on the corresponding standard deviation (SD) was given, we assumed the outcome to have a standard SD that is equal to the highest SD, after it has been approximately matched for sample size with the study from where the SD is borrowed. We planned to explore the robustness of this decision separately by sensitivity analysis.

Assessment of heterogeneity

We carried out meta-analyses when studies were sufficiently homogeneous in terms of their clinical and methodological characteristics. In addition to visual inspection of the forest plots, we used the I^2 statistic to quantify any heterogeneity in the meta-analysis (Higgins 2011). For I^2 statistic levels up to 50%, we considered heterogeneity to be mild to moderate. For I^2 statistic levels between 50% and 80%, we considered heterogeneity to be moderate and, where possible, we used random-effects models to allow for heterogeneity. If the I^2 statistic exceeded 80%, we considered heterogeneity to be substantial, and did not present pooled results; instead, we planned to report any observations as a narrative (Higgins 2011).

Assessment of reporting biases

We minimised the risk of reporting bias by undertaking a comprehensive search over multiple electronic databases and additional resources for both unpublished and published articles. We did not impose any language restrictions. We were alert for duplication of data. We were unable to construct a funnel plot to assess publication bias, as there were fewer than 10 studies in any analysis (Higgins 2011).

Data synthesis

We carried out statistical analysis using Review Manager 5 software (RevMan 2014). If the studies were sufficiently similar, we combined the data using a fixed-effect model. If we detected moderate heterogeneity, we used a random-effects model (Higgins 2011).

We meta-analysed dichotomous data using the Mantel-Haenszel method to calculate RRs; and for continuous data we used the MD, or SMD, as appropriate. We meta-analysed time to recurrence data as HRs using the generic inverse variance method.

We planned to use the Peto odds ratio if the obtained data included rare events (as might be the case for adverse events).

We conducted separate analyses according to the route of drug administration (oral, topical, subcutaneous, intramuscular, or intravenous).

Some of the primary studies did not report combined findings for all first-episode participants. For example, separate data were reported for male and female participants, or for first episode of primary infection and first episode of non primary infection. We stratified our analyses as required, to facilitate maximum pooling of data.

Subgroup analysis and investigation of heterogeneity

Where data were available, we conducted subgroup analyses to determine the separate evidence within the following subgroups.

1. Gender.
2. Length of treatment (five days or less, more than five days). The rationale for this subgroup was that the usual recommended length of treatment is five days with no evidence of benefit for longer periods of time (Azwa 2009).
3. Type of drug within a class
4. Duration of time between appearance of lesions and initiation of treatment (five days or less, more than five days). The rationale for this subgroup was that it is usually recommended that treatment be initiated as soon as possible once a clinical diagnosis has been made (Azwa 2009).
5. Immunodeficiency e.g. HIV.
6. First episode of primary infection versus first episode of non-primary infection.

If we detected substantial statistical heterogeneity, we explored clinical and methodological differences between the studies that might account for this. We took any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions to arbitrary decisions made regarding the eligibility and analysis were robust. These analyses included consideration of whether the review conclusions would have differed if:

1. eligibility were restricted to studies without high risk of bias;
2. a random-effects model had been adopted; and
3. imputed data were included by ITT.

Overall quality of the evidence: 'Summary of findings' table

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEproGDT software (GRADEproGDT 2015).We justified all decisions to down- or up-grade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.We then imported these tables into Review Manager 5 (RevMan 2014).

We included the following outcomes in the 'Summary of findings' tables: Duration of symptoms from onset of treatment, Adverse events, Duration of lesions from onset of treatment and Time to recurrence.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

We conducted the searches in April 2016. The searches were broad and included antiviral medications. After de-duplication we had 3349 studies. After extensive screening and assessment, we identified 26 studies eligible for inclusion in this review (see Figure 1). Two studies are awaiting classification (see Characteristics of studies awaiting classification table). We have not identified any ongoing studies in this area.

Figure 1. Study flow diagram.

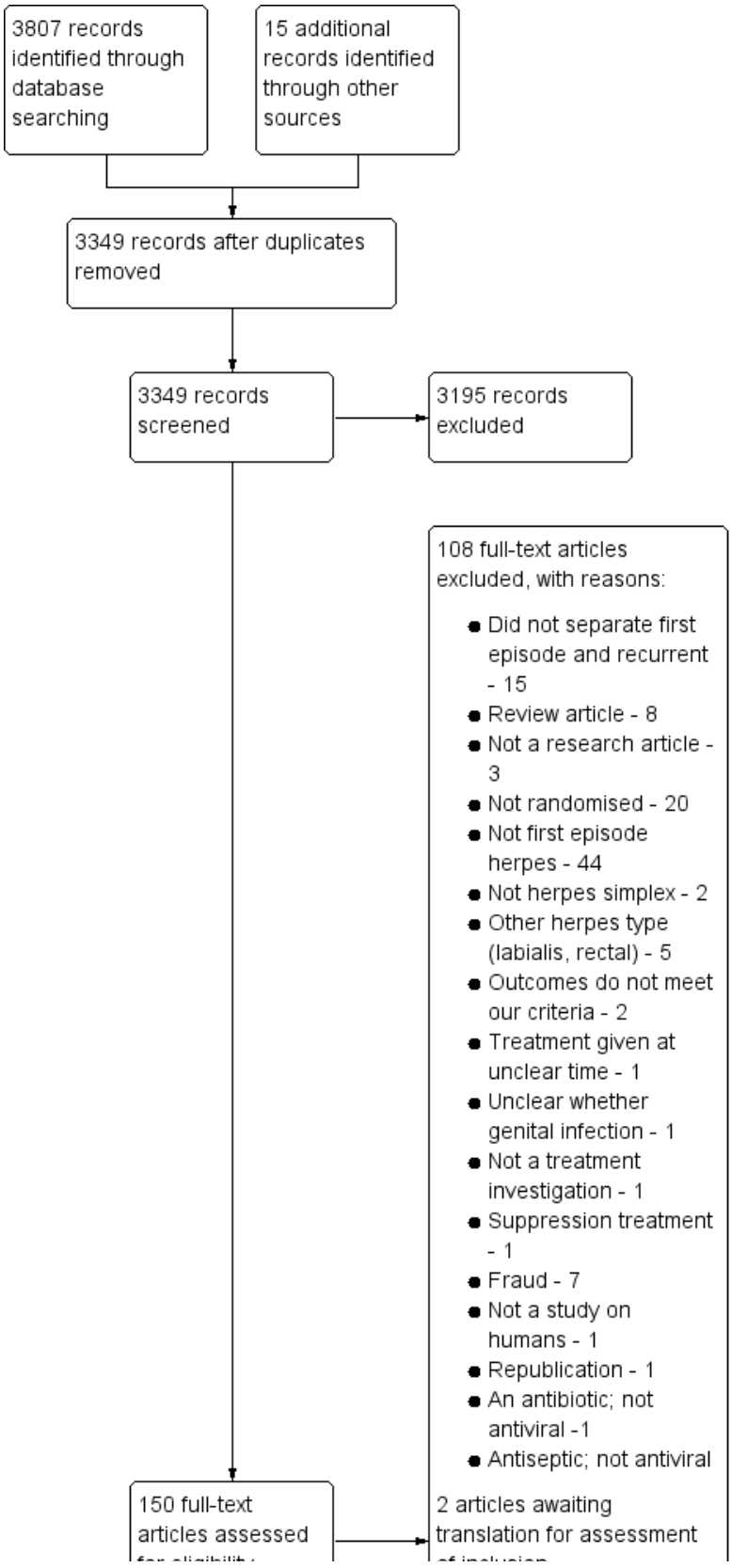
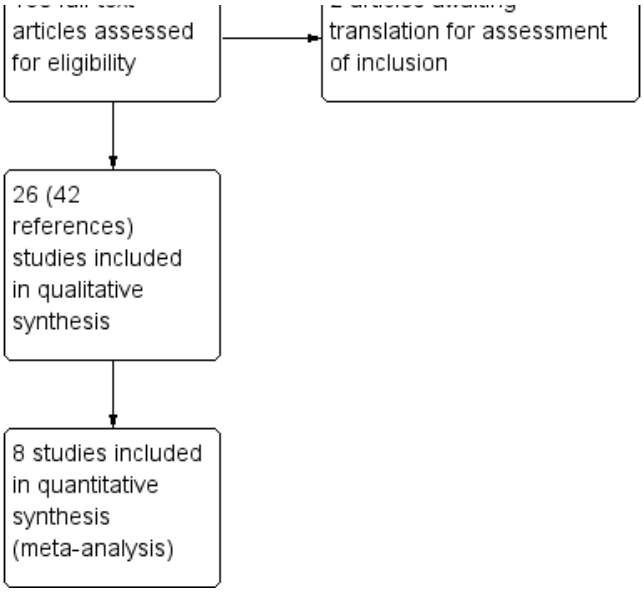


Figure 1. (Continued)



Included studies

Design and setting of the included studies

We included 26 studies (documented by 42 publications) which analysed 2084 participants. Most of the studies were conducted in the US (Adams 1976; Bryson 1983; Corey 1982a; Corey 1982b; Corey 1983; Levin 1989; Mertz 1984; Pazin 1987; Peacock 1988; Silvestri 1982; Wald 1994), and the UK (Csonka 1984; Fiddian 1983; Kinghorn 1986a; Kinghorn 1986b; Mindel 1982; Mindel 1986; Mindel 1987), with additional studies in New Zealand (Batcheler 1986), Canada (Mendelson 1986), China (Lai 2000), Sweden (Nilsen 1982), Mexico (Zavala 1988), and Japan (Niimura 1996); one multicentre study included participants from the US, UK, and Australia (Fife 1997). The largest study included 643 participants (Fife 1997), and the smallest study included 11 (Csonka 1984). Overall, the studies were not recent, with the oldest study published in 1976 (Adams 1976), and the newest study published in 2000 (Lai 2000).

Sixteen studies stated that they received commercial funding (Corey 1982a; Corey 1982b; Corey 1983; Fiddian 1983; Fife 1997; Kinghorn 1986a; Kinghorn 1986b; Levin 1989; Mendelson 1986; Mertz 1984; Mindel 1982; Mindel 1986; Mindel 1987; Nilsen 1982; Peacock 1988; Wald 1994). Four studies apparently received no commercial funding (Adams 1976; Csonka 1984; Pazin 1987; Silvestri 1982). Six studies did not mention their funding source (Altomare 1985; Batcheler 1986; Bryson 1983; Lai 2000; Niimura 1996; Zavala 1988).

Participants in the included studies

Three studies included only women (Batcheler 1986; Mindel 1986; Pazin 1987), and the remaining 23 studies included men and women.

The duration of symptoms required for participant eligibility differed between studies. These criteria are presented in Table 1.

- Adams 1976 and Altomare 1985 included participants with onset of symptoms of less than two days.
- Fife 1997, Pazin 1987, and Zavala 1988 included participants with onset of symptoms of less than three days.
- Levin 1989 included participants with onset of symptoms of less than four days.
- Csonka 1984, Fiddian 1983, Lai 2000, Mendelson 1986, Mindel 1986, Mindel 1987, Nilsen 1982, and Wald 1994 included participants with onset of symptoms of less than five days.
- Bryson 1983, Corey 1982a, Corey 1982b, Kinghorn 1986a, Kinghorn 1986b, Mertz 1984, and Mindel 1982 included participants with onset of symptoms of less than six days.
- Corey 1983 and Peacock 1988 included participants with onset of symptoms of less than seven days.
- Silvestri 1982 included participants with onset of symptoms of less than eight days.
- Batcheler 1986 did not state how many days of symptoms their participants had before treatment
- Niimura 1996 included from day 2, 3, 4, 5, 6, 7 or more, but subgrouped data of results was not available.
- Bryson 1983, Corey 1982a, and Corey 1982b subgrouped by antibody status (first episode of primary infection and first episode of non-primary infection).
- It is important to note that Mindel 1982 only included participants with severe first episode genital herpes.
- Adams 1976, Bryson 1983, Fiddian 1983, Kinghorn 1986b, and Nilsen 1982 looked at both males and females and did not provide results subgrouped by antibody status.
- The remaining studies did not report results by either gender or antibody status.

Interventions in the included studies

Antiviral versus placebo

- Oral acyclovir versus placebo (Bryson 1983; Kinghorn 1986b; Mertz 1984; Nilsen 1982). Some participants in both arms of Kinghorn 1986b also received co-trimoxazole. The oral dose of acyclovir was 1 gm daily in most studies.
- Oral ribavirin versus placebo (Zavala 1988).

- Intravenous acyclovir versus placebo (Corey 1983; Mindel 1982; Peacock 1988).
- Topical acyclovir versus placebo (Corey 1982a; Corey 1982b; Fiddian 1983; Kinghorn 1986a).
- Topical cycloxolone versus placebo (Csonka 1984).
- Topical carbenoxolone versus placebo (Csonka 1984).
- Topical tromantadine versus placebo (Altomare 1985).
- Topical adenosine arabinoside versus placebo (Adams 1976).
- Topical idoxuridine in dimethyl sulfoxide versus dimethyl sulfoxide alone or saline (Silvestri 1982).

Antiviral versus other antiviral

- Oral valaciclovir versus acyclovir (Fife 1997; Lai 2000).
- Topical 2% carbenoxolone cream versus 2% cicloxolone cream (Csonka 1984).
- Oral acyclovir versus inosine prabonex (with or without oral acyclovir in control arm) (Mindel 1987).

Antiviral regimen comparisons

- Long versus short course oral acyclovir (Mindel 1986).
- High (4 gm/day) versus standard dose (1 gm/day) oral acyclovir (Wald 1994).
- Famciclovir at doses, 125 mg, 250 mg and 500 mg (Niimura 1996).

Antiviral versus interferon

- Topical acyclovir versus intramuscular interferon (Levin 1989).

Interferon versus placebo

- Intramuscular interferon versus placebo (Pazin 1987).
- Topical interferon versus placebo (Batcheler 1986).
- Subcutaneous interferon versus placebo (Mendelson 1986).

We did not find any studies of imiquimod, antiviral + natural product, or natural products that met the inclusion criteria.

Outcomes in the included studies

Primary outcomes

1. Duration of symptoms from onset of treatment

Most studies reported duration of symptoms, but many either reported only median values (Corey 1983; Fiddian 1983; Mertz 1984; Mindel 1982; Mindel 1986; Mindel 1987; Nilsen 1982; Peacock 1988; Wald 1994), or reported dichotomous data (e.g. number healed by six days) (Csonka 1984; Niimura 1996). We could not meta-analyse these data.

Other studies reported means, but some failed to report standard deviations (SDs) or standard errors (SEs) (Adams 1976; Bryson 1983; Fife 1997; Mendelson 1986; Silvestri 1982), and so we had to impute the SD or report the data in additional tables. Only one study reported hazard ratios for this outcome (Fife 1997).

2. Time to first recurrence

Nine studies reported time to first recurrence (Bryson 1983; Corey 1982a; Corey 1982b; Mendelson 1986; Mertz 1984; Mindel 1987; Pazin 1987; Peacock 1988; Wald 1994), but none reported hazard ratios. Six of these studies reported median time to first recurrence (Bryson 1983; Corey 1982a; Corey 1982b; Mertz 1984; Mindel 1987; Wald 1994). Mean times were given by Peacock 1988, but the remaining two studies just declared there were no differences in time to first recurrence between the two groups and did not provide numerical data (Mendelson 1986; Pazin 1987). The proportion of participants who were adequately followed up varied across studies, but was around 80% in those that declared numbers of patients followed up (Corey 1982a; Corey 1982b; Wald 1994); however, the majority of studies did not declare the number of patients adequately followed up.

3. Adverse events

Nearly all studies reported adverse events. Many failed to report comparative data, but this was often because (as they reported in the text) there were no adverse events reported in either arm. Although, one study reported other outcomes separately for first-episode participants, for this particular outcome separate data were not provided (Altomare 1985) .

Secondary outcomes

1. Duration of lesions from onset of treatment

Most studies reported duration of lesions, although as noted above, many reported data unsuitable for meta-analysis.

2. Neonatal effects

No studies reported this outcome.

3. Caesarean section delivery

No studies reported this outcome.

Excluded studies

We excluded 106 studies; the reasons are reported in the Characteristics of excluded studies table. Common reasons for exclusion are that the studies were not looking at first-episode genital herpes, or the study design did not appear to be randomised.

We excluded seven studies due to suspected fraudulent publication (Syed 1995a; Syed 1995b; Syed 1995c; Syed 1997a; Syed 1997b; Syed 1998a; Syed 1998b). When we attempted to gain more information from T. A. Syed regarding his studies, we discovered that he is currently serving a prison sentence for 64 counts including practicing medicine without a license, grand theft, perjury, and forgery. It appears he was never employed at universities he claimed the research was from. Other authors listed on his studies were unable to be identified. For these reasons we have chosen not to include these studies despite the fulfilment of the inclusion criteria of this review. Our Review Group has contacted all relevant journals where his studies were published to highlight this information.

Risk of bias in included studies

We rated most of the studies at unclear risk of bias in most domains. We attempted to contact all trial authors for more information about randomisation and blinding procedures. For a graphical representation of the results of the risk of bias assessment see Figure 2 and Figure 3 .

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

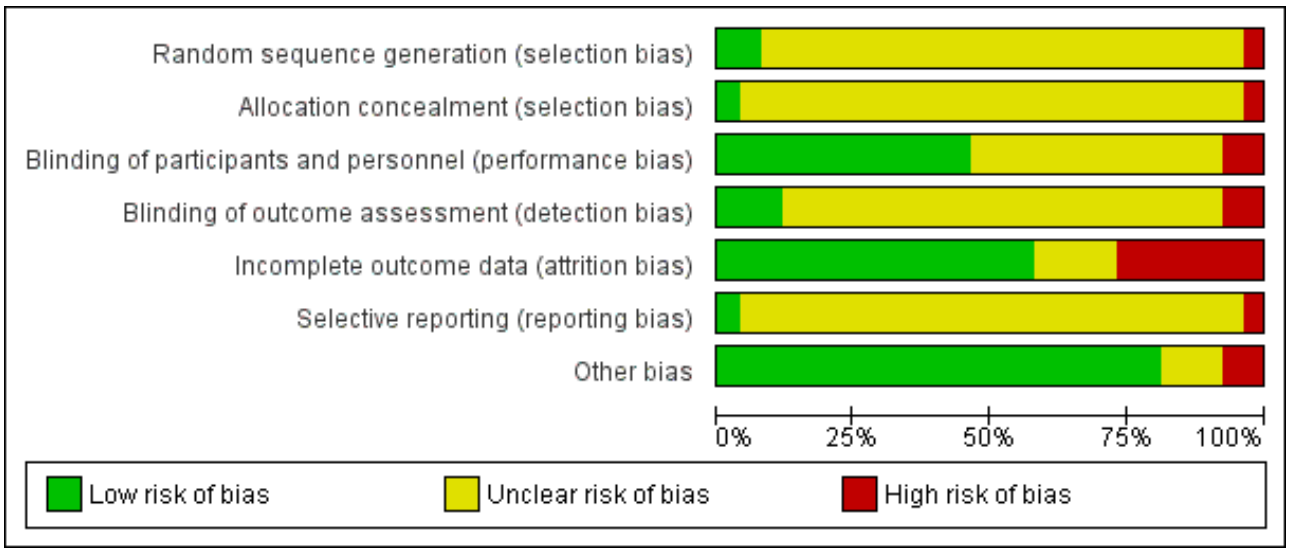


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

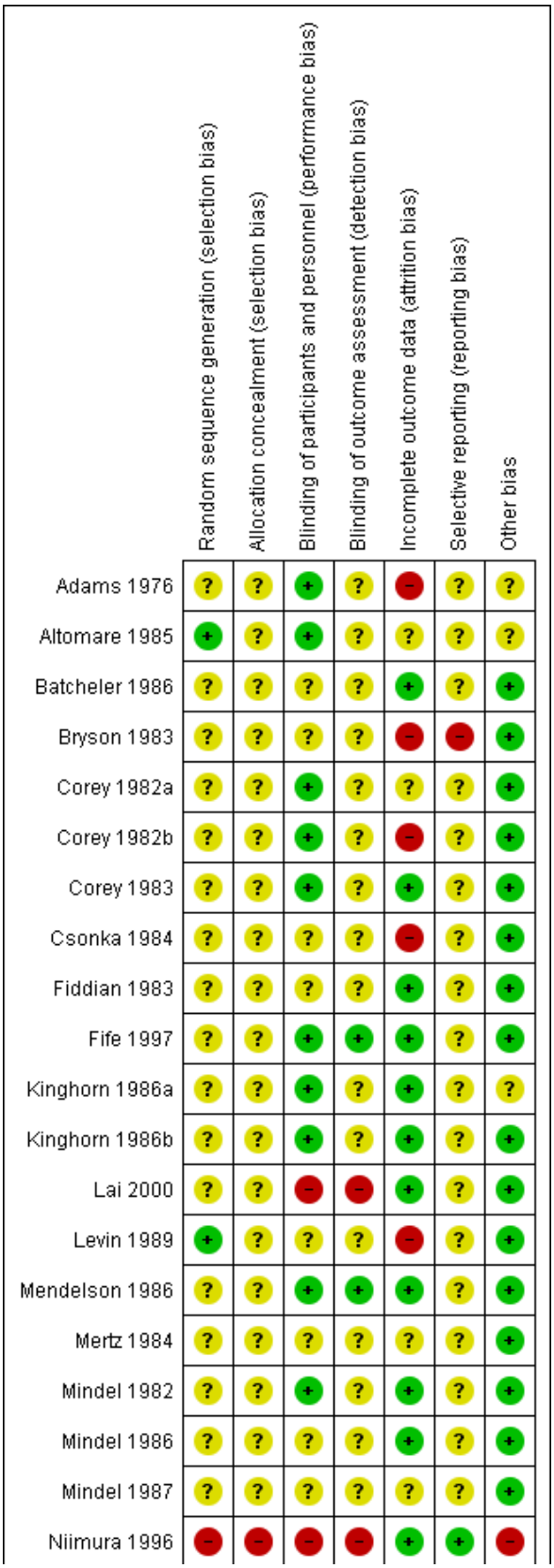
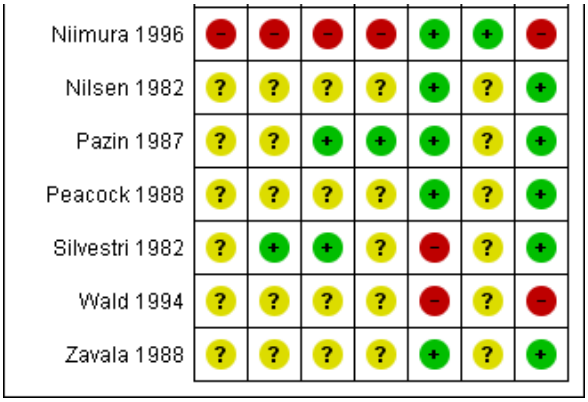


Figure 3. (Continued)



Allocation

Generation of random sequence

Only two studies (8%) reported acceptable methods of random sequence generation (Altomare 1985; Levin 1989). We judged one study (4%) to be at high risk of bias (Niimura 1996), and the remaining studies (88%) at unclear risk of bias in this domain.

Allocation concealment

Only one study (4%) reported acceptable methods of allocation concealment (Silvestri 1982). We judged one study (4%) to be at high risk of bias (Niimura 1996), and the remaining studies (92%) at unclear risk of bias in this domain.

Blinding

Twelve studies (46%) described acceptable methods of blinding of participants and study personnel (Adams 1976; Altomare 1985; Corey 1982a; Corey 1982b; Corey 1983; Fife 1997; Kinghorn 1986a; Kinghorn 1986b; Mendelson 1986; Mindel 1982; Pazin 1987; Silvestri 1982). We judged two studies (8%) at high risk of bias in this domain (Lai 2000; Niimura 1996), and the remaining studies (46%) at unclear risk; many of these studies mentioned that they were double-blinded but failed to provide further details.

Only three studies (12%) described acceptable methods of blinding of outcome assessment (Fife 1997; Mendelson 1986; Pazin 1987). We judged two studies (8%) at high risk of bias in this domain (Lai 2000; Niimura 1996), and the remaining studies (80%) at unclear risk; many of these studies mentioned that they were double-blinded but failed to provide further details.

Incomplete outcome data

Fifteen studies (58%) analysed all or most randomised participants for at least two of our primary outcomes and we judged these at low risk of attrition bias (Batcheler 1986; Corey 1983; Fiddian 1983; Fife 1997; Kinghorn 1986a; Kinghorn 1986b; Lai 2000; Niimura 1996; Mendelson 1986; Mindel 1982; Mindel 1986; Nilsen 1982; Pazin 1987; Peacock 1988; Zavala 1988). We judged seven studies (27%) at high risk of bias, in most cases because they failed to analyse a high proportion (< 20%) of randomised participants (Adams 1976; Bryson 1983; Corey 1982b; Csonka 1984; Levin 1989; Silvestri 1982; Wald 1994). We judged the remaining studies (15%) at unclear risk of bias in this domain (Altomare 1985; Corey 1982a; Mertz 1984; Mindel 1987).

In the studies reporting time to first recurrence, the proportion of participants who were adequately followed-up varied across the studies see Description of studies.

Selective reporting

We judged one study (4%) at high risk of bias in this domain as it was unclear why outcomes were not reported for one group of randomised participants (Bryson 1983); we judged all other studies (96%) at unclear risk of selective reporting, as study protocols were not available and there was no statement in the publication stating that all measured outcomes had been reported. Therefore it was unclear whether all prespecified outcomes were reported.

Other potential sources of bias

We judged two studies (8%) at high risk of bias for this domain. One study was due to baseline imbalance (Wald 1994), and one study was due to the data and analyses being undertaken by the funder (Niimura 1996). We rated three studies (12%) at unclear risk of other bias, for example, due to changes in the intervention during the study, or possible co-intervention (Adams 1976; Altomare 1985; Kinghorn 1986a). We judged all other studies (80%) at low risk of bias in this domain, as no potential source of other bias was identified.

Effects of interventions

See: **Summary of findings for the main comparison** Oral acyclovir versus placebo for men and women with their first episode of genital herpes; **Summary of findings 2** Topical acyclovir versus placebo for men and women with their first episode of genital herpes

Antiviral versus placebo

1.1 Oral acyclovir versus placebo

Four studies with 227 participants were included in this comparison (Bryson 1983; Kinghorn 1986b; Mertz 1984; Nilsen 1982).

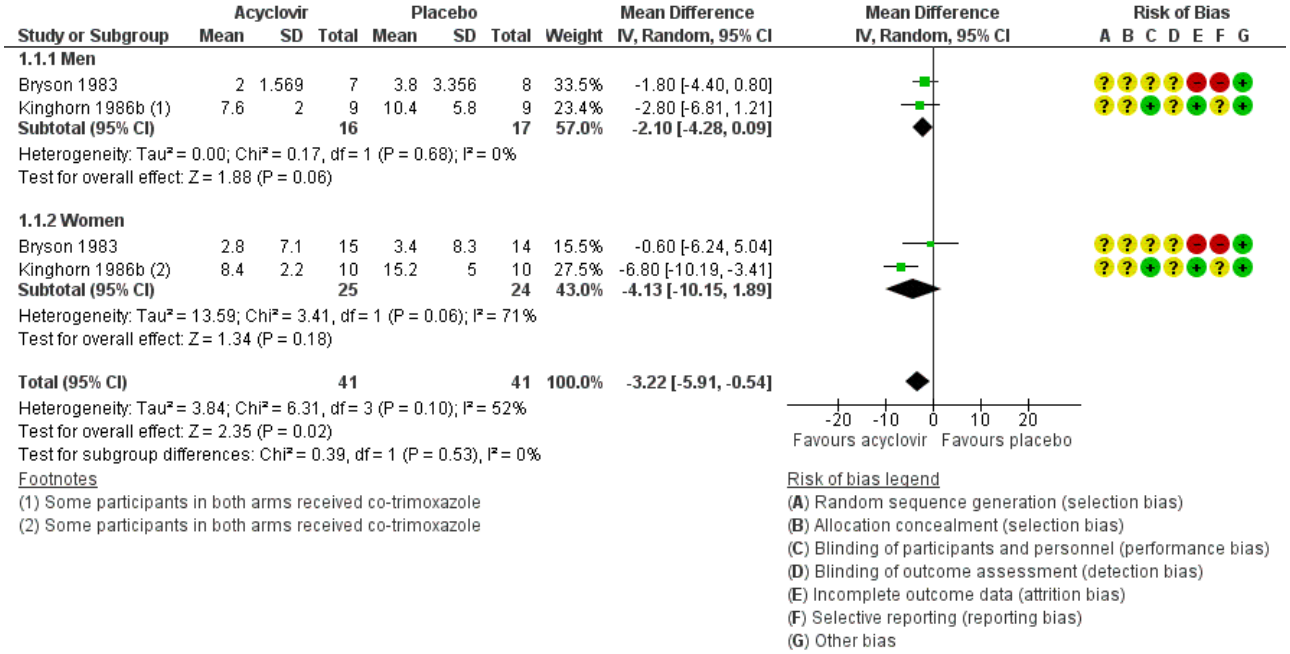
Primary outcomes

1.1.1 Duration of symptoms from onset of treatment

When two studies were pooled, symptom duration was significantly shorter in the acyclovir group (Bryson 1983; Kinghorn 1986b) (mean difference (MD) -3.22 days, 95% confidence interval (CI) -5.91 to -0.54; two RCTs, 82 participants, I^2 statistic = 52%) (Analysis 1.1;

Figure 4). There was moderate heterogeneity for this outcome for which there was no clear explanation. Use of a random-effects model did not affect the significance of the findings.

Figure 4. Forest plot of comparison: 1 Oral acyclovir versus placebo, outcome: 1.1 Duration of symptoms from onset of treatment.



Two studies reported medians only (Mertz 1984; Nilsen 1982). One found that the duration of symptoms was significantly shorter in the acyclovir group than in the placebo group among participants (n = 101) with first episode of primary infection (P < 0.5) (Mertz 1984). There was no significant difference between the groups in participants with first episode of non-primary infection (n = 13). The other study found that the duration of symptoms was significantly shorter in the acyclovir group (Nilsen 1982) (n = 31, P < 0.05). See Table 2.

Due to the moderate heterogeneity (52%), we used a random-effects model for this analysis. The evidence for this outcome was of low quality. We downgraded the quality of evidence due to the risk of bias of associated studies and because this finding is based on very low sample numbers (Summary of findings for the main comparison).

Subgroup analysis by gender

When we pooled Bryson 1983 and Kinghorn 1986b, and considered men and women separately, for males there is a difference in the duration of symptoms after treatment with acyclovir (MD -2.10 days, 95% CI -4.28 to 0.09; 2 RCTs, 33 men, I^2 statistic = 0%). In females there was high heterogeneity between the two trials included in the meta analysis and it did not show any statistical difference between those taking acyclovir and those taking placebo (MD -4.13 days, 95% CI -10.15 to 1.89; 2 RCTs, 49 women, I^2 statistic = 71%). However overall, we did not observe any statistical difference between men and women (Test for subgroup differences: Chi^2 = 0.39, P = 0.53) for the duration of symptoms from onset of treatment.

When median duration of symptoms was subgrouped by gender in Nilsen 1982, findings remained statistically significant among males (n = 14, P < 0.05) but not among females (n = 17). See Table 2.

These subgroup findings should be regarded with caution and are as a result of low to very low quality evidence due to the small sample sizes, heterogeneity in one of the female subgroups, and inconsistency in the findings.

Subgroup analysis by antibody status (first episode of primary infection or first episode of non-primary infection)

No data were available to allow subgrouping by antibody status. However, one study that had reported medians did report these two groups separately (Mertz 1984). This study showed a significant reduction in duration of symptoms for those undergoing their first episode of primary infection as indicated by their antibody status. In those whose antibody status indicated a previous infection, there was no observed reduction (Table 2).

1.1.2 Time to first recurrence

No studies reported hazard ratios. Two studies reported no significant difference between the two groups in the median days to recurrence among participants with adequate follow-up (Bryson 1983; Mertz 1984). See Table 2.

1.1.3 Adverse events

Very few adverse events were reported (Analysis 1.2). Reported events included headache, nausea, heartburn, fatigue, and sore throat. Two studies reported that no adverse events occurred in either group (Bryson 1983; Kinghorn 1986b). This evidence was of

low quality as there was a high level of heterogeneity and the risk of bias of the included studies was unclear for most of the domains (Summary of findings for the main comparison).

Secondary outcomes

1.1.4 Duration of lesions from onset of treatment

When we pooled two studies (Bryson 1983; Kinghorn 1986b), lesion duration was significantly shorter in the acyclovir group (MD -3.51 days, 95% CI -6.19 to -0.82; two RCTs, 86 participants, I^2 statistic = 0%, Analysis 1.3).

Two studies reported medians only (Mertz 1984; Nilsen 1982). One study found that the duration of lesions was significantly shorter in the acyclovir group than in the placebo group among participants (n = 119) with first episode of primary infection (P < 0.01) (Mertz 1984). There was no significant difference between the groups for participants with first episode of non-primary infections (n = 31). The other study found that the duration of symptoms was significantly shorter in the acyclovir group (n = 31, P < 0.01) (Nilsen 1982). See Table 2. These findings should be regarded with caution due to the low quality evidence shown here. This is a result of small sample sizes and high levels of bias associated with the included studies (Summary of findings for the main comparison).

Subgroup analysis by gender

When we pooled Bryson 1983 and Kinghorn 1986b, and considered men and women separately, for males there is a difference in the duration of lesions after treatment with acyclovir (MD -5.74 days, 95% CI -9.80 to -1.69; 35 men, I^2 statistic = 0%). In females the meta analysis did not show any statistical difference between those taking acyclovir and those taking placebo for duration of lesions (MD -1.74 days, 95% CI -5.34 to 1.85; 51 women, I^2 statistic = 0%). However overall, we did not observe any statistical difference between men and women (Test for subgroup differences: Chi^2 = 2.10, P = 0.15) for the duration of lesions from onset of treatment.

However, when findings were subgrouped by gender in Nilsen 1982 (data supplied as medians), among males there was no difference between the acyclovir and placebo groups (n = 14, P = 0.06), but among females there was a significantly shorter lesion duration in the acyclovir group (n = 17, P < 0.05). See Table 2.

These subgroup findings should be regarded with caution due to the low grade of the evidence as a result of small sample sizes and inconsistency in the findings.

Subgroup analysis by antibody status (first episode of primary infection or first episode of primary non-primary infection)

No data were available to allow subgrouping by antibody status. However, one study that had reported medians did report these two groups separately (Mertz 1984). This study showed a significant reduction in duration of lesions for those undergoing their first episode of primary infection, as indicated by their antibody status. In those whose antibody status indicated they were having a first episode of non primary infection, there was no observed reduction (Table 2).

No other secondary outcomes were reported.

1.2 Oral ribavirin versus placebo

One study made this comparison (Zavala 1988). The study was in Spanish, and the data were provided by a translator.

Primary outcomes

1.2.1 Duration of symptoms from onset of treatment

The mean duration of symptoms from the onset of treatment for the treatment group of 30 patients was 5.7 days, and for the placebo group of 30 patients was 15.5 days. No standard errors were provided, so we have reported the available data in Table 3.

Our other primary outcomes were not reported.

Secondary outcomes

Our other secondary outcomes were not reported.

1.3 Intravenous acyclovir versus placebo

Three studies compared this outcome (Corey 1983; Mindel 1982; Peacock 1988). Nearly all outcomes were reported as median values. Peacock 1988 reported mean values for time to first recurrence but did not report standard deviations. Mindel 1982 only included patients with severe first episode of primary infection genital herpes that warranted hospital admission.

Primary outcomes

1.3.1 Duration of symptoms from onset of treatment

Two studies reported a shorter median duration of symptoms in the acyclovir group (Mindel 1982: n = 30, P < 0.05; Peacock 1988: n = 82, P = 0.019). The third study reported no significant difference between the groups (Corey 1983: n = 31, P = 0.17). See Table 4.

Subgroup analysis by gender

One study reported data for females only (n = 24) and found no significant difference between the acyclovir and the placebo group (Mindel 1982; Table 4).

Subgroup analysis by antibody status (first episode of primary infection or first episode of non-primary infection)

One study reported data separated into first episode of primary infection and first episode of non-primary infection based on antibody status (Peacock 1988). Acyclovir reduced the symptoms in the first episode of primary infection group only, and no difference was seen in the first episode of non-primary infection group (Table 4).

1.3.2 Time to first recurrence

One study reported mean time to first recurrence (Peacock 1988). No measurement of error was provided for this information but this study observed a mean time to first recurrence in the acyclovir group of 89 days and 93 days in the placebo group.

Corey 1983 and Mindel 1982 combined their data in a follow-up publication, subgrouped into participants with HSV-1 infection (n = 14) and those with HSV-2 infection (n = 46). They reported no significant difference (P = 0.04) between the groups in median time to first recurrence. See Table 4.

1.3.3 Adverse events

None of the three studies reported a difference between the groups in the rate of adverse events, though sample sizes were small for individual outcomes (Analysis 2.1). Reported events included mild phlebitis or pain at the infusion site, rashes, abnormal liver function tests, nausea, vomiting, and dizziness. Some of these effects were attributed to co-administration of codeine.

Secondary outcomes

1.3.4 Duration of lesions from onset of treatment

All three studies reported a shorter median duration of lesions in the acyclovir group (Mindel 1982: n = 30, P < 0.001; Peacock 1988: n = 82, P = 0.02; Corey 1983: n = 31, P = 0.002). See Table 4.

Subgrouped by gender

One study reported data for females only (n = 24) and found a significantly shorter median duration of lesions in the acyclovir group (P < 0.05) (Mindel 1982; Table 4).

Subgroup analysis by antibody status (first episode of primary infection or first episode of non-primary infection)

One study reported data separated into first episode of primary infection and first episode of non-primary infection based on antibody status. Acyclovir reduced the duration of lesions in the first episode of primary infection group (P < 0.015) but not in the first episode of non-primary infection group (Peacock 1988; Table 4).

No other secondary outcomes were reported.

1.4 Topical acyclovir versus placebo

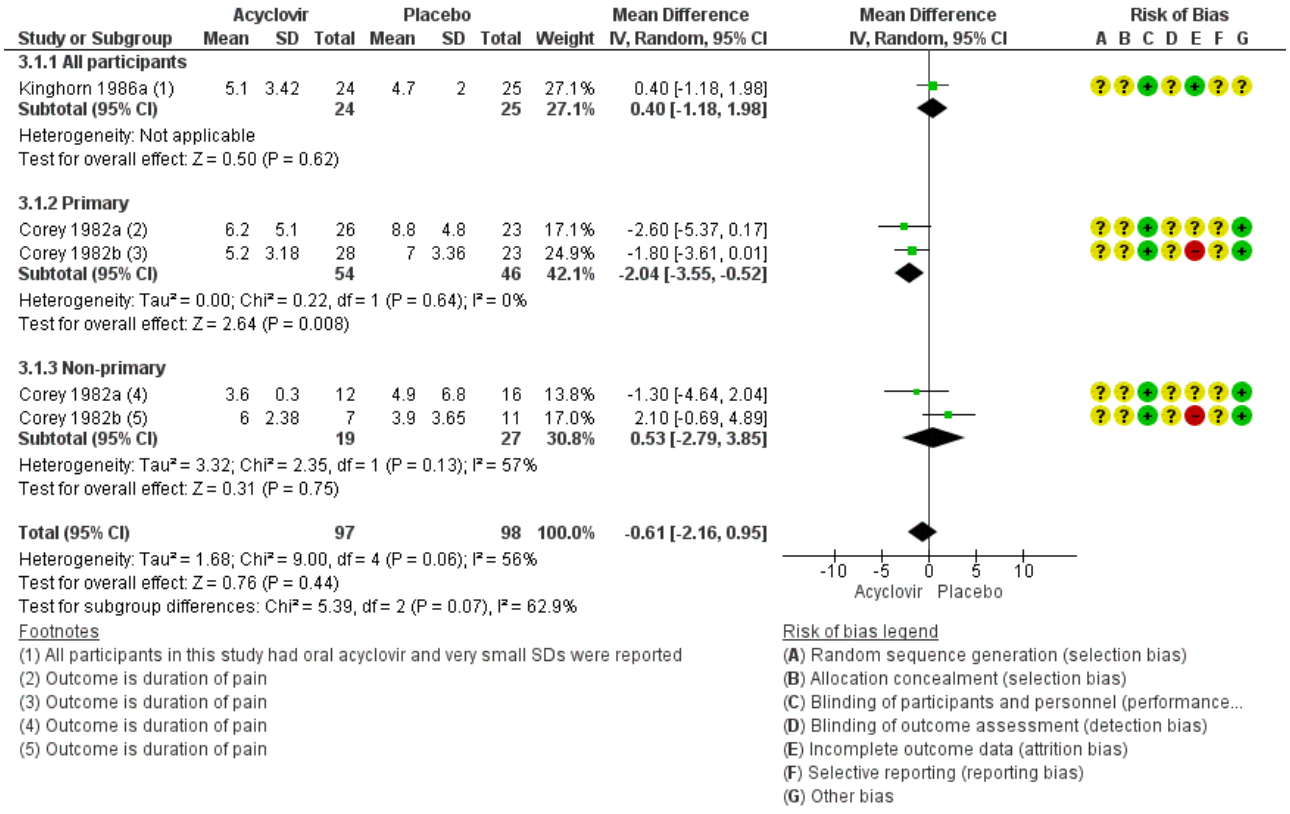
Four studies made this comparison (Corey 1982a; Corey 1982b; Fiddian 1983; Kinghorn 1986a). It should be noted that in the Kinghorn 1986a study all participants received oral acyclovir in addition to the topical acyclovir or placebo.

Primary outcomes

1.4.1 Duration of symptoms from onset of treatment

When three studies were pooled, there was no difference between the groups in symptom duration (Corey 1982a; Corey 1982b; Kinghorn 1986a) (MD -0.61 days, 95% CI -2.16 to 0.95; 3 RCTs, 195 participants, I^2 statistic = 56%; Analysis 3.1; Figure 5). As there was moderate heterogeneity for this analysis for which there was no obvious explanation, we used a random-effects model.

Figure 5. Forest plot of comparison: 4 Topical acyclovir versus placebo, outcome: 4.1 Duration of symptoms from onset of treatment.

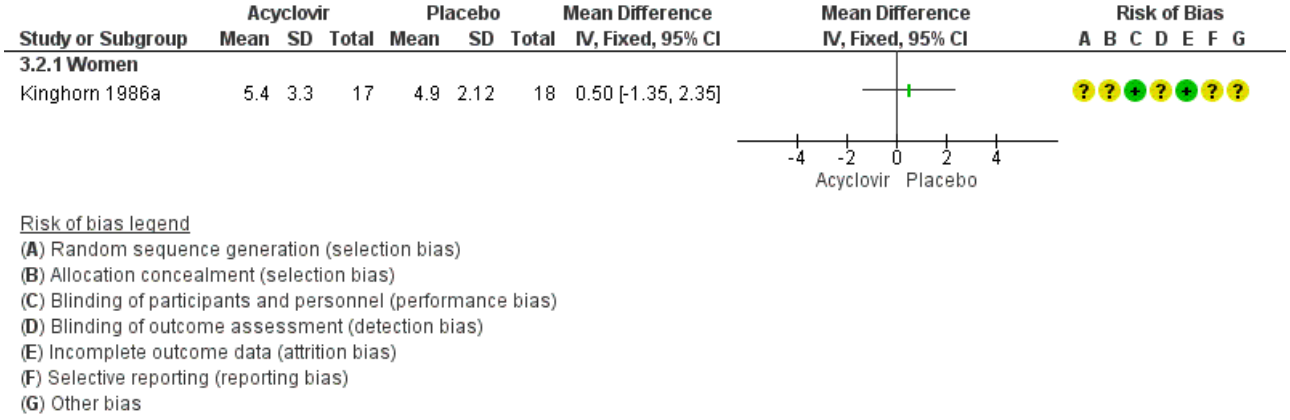


One study reported medians only (Fiddian 1983). The duration of symptoms was significantly shorter in the acyclovir group than in the placebo group (n = 101, P = 0.01; see Table 5). We graded this evidence as low quality due to the high risk of bias associated with the included studies and the reasonably high heterogeneity (Summary of findings 2).

Subgrouped analysis gender

Kinghorn 1986a analysed females separately and found no difference between the acyclovir and placebo groups (MD 0.50 days, 95% CI -1.35 to 2.35; 35 women). (See Analysis 3.2; Figure 6). In the study that reported median values only, there was no statistically significant difference between the groups among men (Fiddian 1983, n = 35), but symptom duration was significantly shorter in the acyclovir group among women (Fiddian 1983, 64 women, P < 0.05). See Table 5.

Figure 6. Forest plot of comparison: 4 Topical acyclovir versus placebo, outcome: 4.2 Duration of symptoms from onset of treatment by gender.



1.4.2 Time to first recurrence

Corey 1982b reported no difference in the median time to recurrence among 58 participants (84% of total) who had adequate follow-up; the median was 79 days in both groups, but it was unclear how many in each group were followed up. No further information about time to recurrence was available.

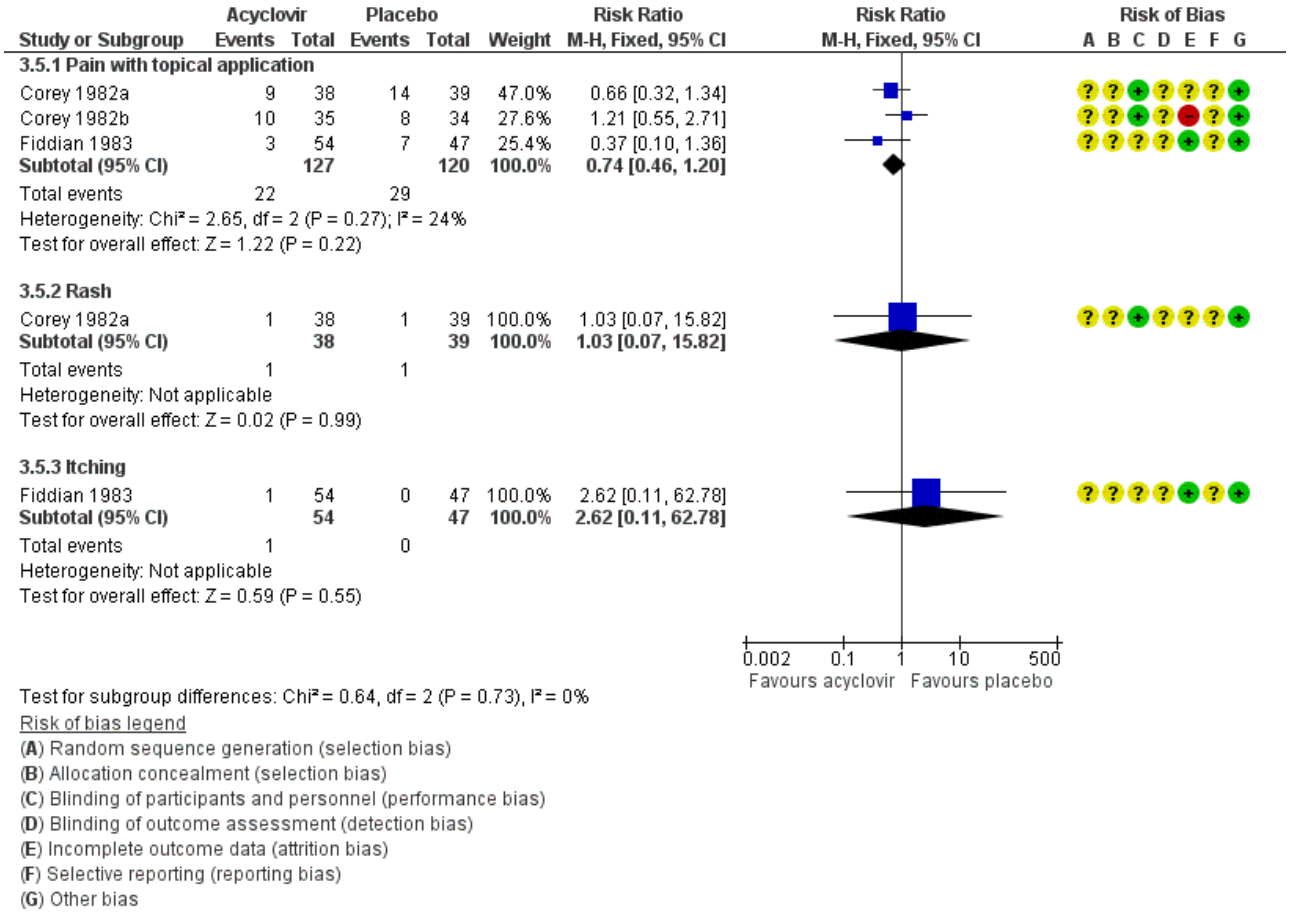
Corey 1982a reported no difference in the median time to recurrence among 25 participants (78% of total) with HSV-2 infection who had adequate follow up; the median was 116 days in both groups, but it was unclear how many in each group were followed up. No further information about time to recurrence was available.

Kinghorn 1986a also failed to show a difference between those on topical acyclovir and those receiving placebo in those who had had a recurrence in the six months following treatment (risk ratio (RR) 1.2, 95% CI 0.6 to 2.3; P = 0.6). Of the 46 patients who completed follow-up, 11 (50%) out of 22 who received acyclovir compared with 10 (42%) out of 24 treated with placebo had a recurrence within six months of their first episode.

1.4.3 Adverse events

None of the studies reported a difference between the groups in the rate of adverse events, though sample sizes were small for individual outcomes (Analysis 3.5, Figure 7). Reported events included pain with topical application, rashes, and itching. This evidence is of moderate quality with the only concern being in regard to the risk of bias associated with the included studies (Summary of findings 2).

Figure 7. Forest plot of comparison: 4 Topical acyclovir versus placebo, outcome: 4.3 Adverse events.

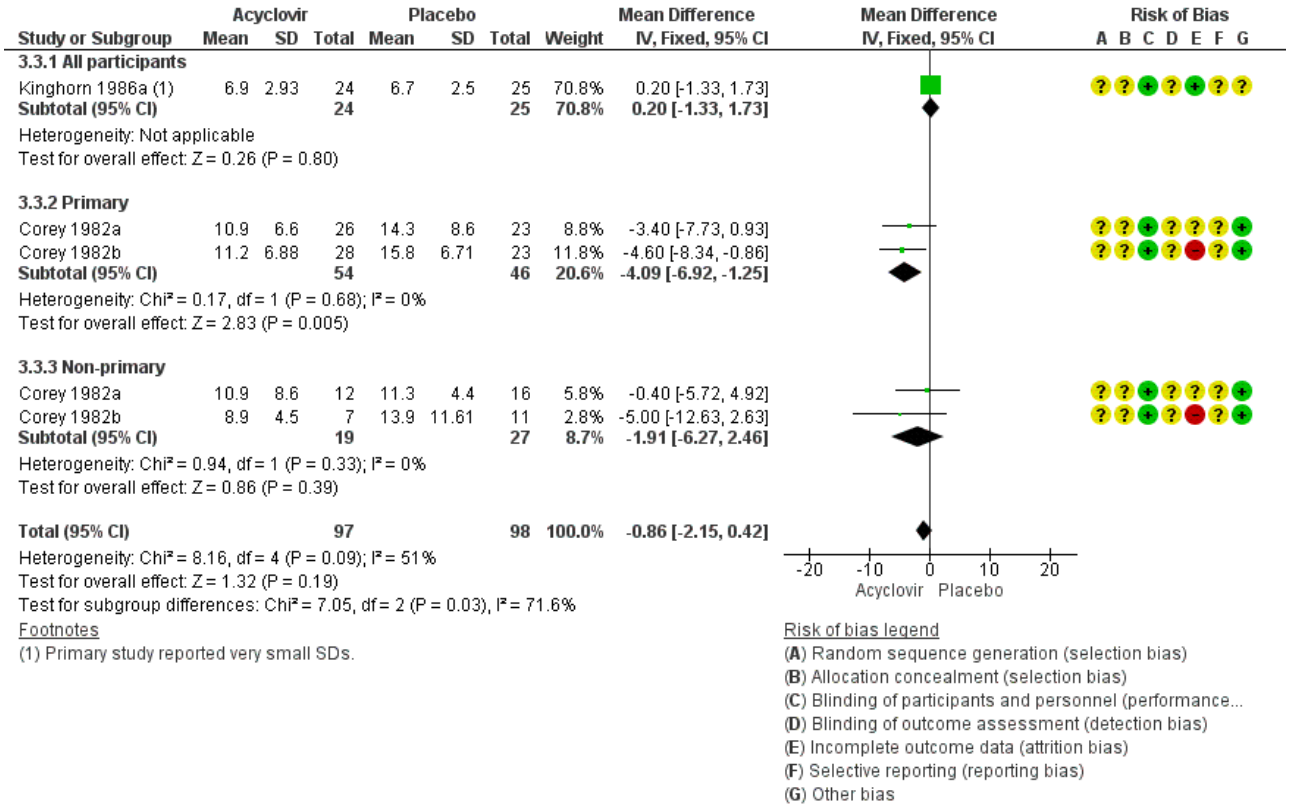


Secondary outcomes

1.4.4 Duration of lesions from onset of treatment by antibody status

When Corey 1982a, Corey 1982b, and Kinghorn 1986a were pooled there was no difference between the groups in lesion duration (MD -0.86 days, 95% CI -2.15 to 0.42; 195 participants, I^2 statistic = 51%, Analysis 3.3; Figure 8). As there was moderate heterogeneity for this outcome for which there was no clear explanation we used a random-effects model.

Figure 8. Forest plot of comparison: 4 Topical acyclovir versus placebo, outcome: 4.4 Duration of lesions from onset of treatment by antibody status.



The study which reported medians only found that the duration of symptoms was significantly shorter in the acyclovir group than in the placebo group (Fiddian 1983, n = 101, P = 0.01; see Table 5). As a result of the substantial heterogeneity and the risk of bias of included studies we have judged this evidence as low quality (Summary of findings 2).

Subgroup analysis by gender

Kinghorn 1986a analysed females as a separate subgroup and found no difference between the acyclovir and placebo groups (MD -0.10 days, 95% CI 1.78 to 1.58; 35 women). See Analysis 3.4.

The study which reported medians only found a significantly shorter lesion duration in the acyclovir group among men (Fiddian 1983) (n = 35, P < 0.01) and also among women (64 women, P < 0.001). See Table 5.

No other secondary outcomes were reported.

1.5 Topical 2% cicloxolone cream versus placebo

One small three-arm study made this comparison (Csonka 1984). It included a total of only 19 participants with first-episode disease, of whom only 11 (57%) were included in the analysis.

Primary outcomes

1.5.1 Duration of symptoms from onset of treatment

There was no difference between the groups in the duration of symptoms at five or seven days. However, no conclusions can be drawn, as analysis included only five participants in the cicloxolone group and four in the placebo group. See Analysis 4.1 and Analysis 4.2.

1.5.2 Time to first recurrence

This outcome was not reported.

5.3 Adverse events

No comparative data were reported among participants with first-episode disease. Among all participants with either first-episode or recurrent genital herpes, one in each group had slight irritation after application of the cream. The reaction was not sufficiently severe to discontinue treatment.

Secondary outcomes

1.5.4 Duration of lesions from onset of treatment

There was no difference between the groups in the duration of lesions at five or seven days. However, no conclusions can be drawn as analysis included only five participants in the cicloxolone group and four in the placebo group. See Analysis 4.3 and Analysis 4.4.

No other secondary outcomes were reported.

1.6 Topical carbenoxolone sodium cream versus placebo

One small three-arm study made this comparison (Csonka 1984). It included a total of only 19 participants with first-episode disease, of whom only 11 (57%) were included in analysis.

Primary outcomes

1.6.1 Duration of symptoms from onset of treatment

There was no difference between the groups in the duration of symptoms at five or seven days. However, no conclusions can be drawn as there were only two participants in the carbenoxolone group and four in the placebo group. See Analysis 5.1 and Analysis 5.2.

1.6.2 Time to first recurrence

This outcome was not reported.

1.6.3 Adverse events

No comparative data were reported among participants with first-episode disease. Among all participants with either first-episode or recurrent genital herpes, one in each group had slight irritation after application of the cream; the reaction was not severe enough to discontinue treatment.

Secondary outcomes

1.6.4 Duration of lesions from onset of treatment

There was no difference between the groups in the duration of lesions at five or seven days. However, no conclusions can be drawn as there were only two participants in the carbenoxolone group and four in the placebo group. See Analysis 5.3 and Analysis 5.4.

Our other secondary outcomes were not reported.

1.7 Topical adenosine arabinoside versus placebo or no treatment

One study made this comparison (Adams 1976). Partway through this study the intervention was changed from adenosine arabinoside topical ointment to gel that was applied topically and intravaginally. Due to poor reporting of study methods, we could not extract data for analysis. The study authors concluded that the intervention was ineffective in both men and women. Available data are presented in Table 6.

1.8 Topical 30% idoxuridine in dimethyl sulfoxide versus dimethyl sulfoxide alone or saline

One study made this comparison but data were not in a format that we could use in a meta-analysis (Silvestri 1982).

Primary outcomes

1.8.1 Duration of symptoms from onset of treatment

There was no difference between the groups in the mean duration of symptoms. See Table 7.

Time to first recurrence

This outcome was not reported.

1.8.2 Adverse events

There was no difference between the groups in the rate of adverse events. Burning on application was reported in both study groups. See Table 7.

Secondary outcomes

1.8.3 Duration of lesions from onset of treatment

There was no difference between the groups in the duration of symptoms. See Table 7.

Our other secondary outcomes were not reported.

1.9 Topical tromantadine versus placebo

One small study made this comparison (Altomare 1985). It included 14 males and seven female participants.

Primary outcomes

1.9.1 Duration of symptoms from onset of treatment

Duration of symptoms and duration of lesions were reported as a combined outcome in this study and data were dichotomous. There was no difference between the groups at three days (Analysis 6.1), six days (Analysis 6.2), or nine days (Analysis 6.3) from onset of treatment, but at 12 days the intervention group were significantly more likely to have healed (RR 2.27, 95% CI 1.04 to 4.97; 1 RCT, 21 participants) (Analysis 6.4).

1.9.2 Time to first recurrence

This outcome was not reported.

1.9.3 Adverse events

Adverse events were poorly reported in this study and no reliable comparative data were available for first-episode participants.

Secondary outcomes

Other secondary outcomes were not reported.

2. Antiviral versus other antiviral

2.1 Oral valaciclovir versus acyclovir

Two studies made this comparison (Fife 1997; Lai 2000). One was a large study which used survival analysis and reported hazard ratios (Fife 1997), and the other small study which reported mean values (Lai 2000).

Primary outcomes

2.1.1 Duration of symptoms from onset of treatment

Both studies reported that there was no difference between the oral valaciclovir group and the oral acyclovir group in the duration of symptoms (hazard ratio (HR) 1.02, 95% CI 0.85 to 1.22; 1 RCT, 643 participants, Analysis 7.1; MD 0.30 days, 95% CI -0.81 to 1.41; 1 RCT, 28 participants, Analysis 7.2).

2.1.2 Time to first recurrence

This outcome was not reported.

2.1.3 Adverse events

There was no difference between the groups in the rate of adverse events. Reported events included nausea and headache, however they were uncommon in both arms of the included studies. See Analysis 7.3.

Secondary outcomes

2.1.4 Duration of lesions from onset of treatment

One study reported this outcome (Fife 1997). There was no significant difference between the groups in the duration of lesions (HR 1.08, 95% CI 0.92 to 1.27; 1 RCT, 643 participants; Analysis 7.4)

Our other secondary outcomes were not reported.

2.2 Topical carbenoxolone sodium versus topical cicloxolone

One small three-arm study made this comparison (Csonka 1984). It included a total of only 19 participants with first-episode disease, of whom only 11 (57%) were included in the analysis.

Primary outcomes

2.2.1 Duration of symptoms from onset of treatment

There was no difference between the groups in the duration of symptoms at five or seven days. However, no conclusions can be drawn as analysis included only two participants in the carbenoxolone group and five participants in the cicloxolone group. See Analysis 8.1.

2.2.2 Time to first recurrence

This outcome was not reported.

2.2.3 Adverse events

No comparative data were reported among participants with first-episode disease. Among all participants with either first-episode or recurrent genital herpes, one in each group had slight irritation after application of the cream. The reaction was not sufficiently severe to discontinue treatment.

Secondary outcomes

2.2.4 Duration of lesions from onset of treatment

There was no difference between the groups in the duration of lesions at five or seven days. However, no conclusions can be drawn as analysis included only two participants in the carbenoxolone group and five participants in the cicloxolone group. See Analysis Analysis 8.2.

Our other secondary outcomes were not reported.

2.3 Oral acyclovir alone versus inosine prabonex with or without acyclovir

One study with 52 participants compared acyclovir alone versus inosine prabonex with or without acyclovir (Mindel 1987). It reported median values.

Primary outcomes

2.3.1 Duration of symptoms from onset of treatment

There was no significant difference between any of the groups in duration of symptoms. See Table 8.

Subgroup analysis by gender

When analysis was restricted to women only, duration of symptoms was significantly shorter in the acyclovir-only group (n = 21) than in the inosine prabonex-only group (n = 24) (P < 0.05), but did not differ from the group receiving both interventions (n = 21). See Table 8.

2.3.2 Time to first recurrence

The authors reported that there was no significant difference between the groups in time to first recurrence. It was not stated what proportion of participants were followed up for this outcome. See Table 8.

2.3.3 Adverse events

The study authors stated that no adverse effects were noted.

Secondary outcomes

2.3.4 Duration of lesions from onset of treatment

Duration of lesions was significantly shorter in the group receiving acyclovir only (n = 24) than in those receiving inosine prabonex only (n = 28). There was no difference between the groups when the group receiving acyclovir only (n = 24) was compared with those receiving acyclovir plus inosine prabonex (n = 49). See Table 8.

Subgroup analysis by gender

When analysis was restricted to women only, duration of lesions did not significantly differ between any of the groups. See Table 8.

Our other secondary outcomes were not reported.

3. Antiviral regimen comparisons

3.1 Long course versus short course acyclovir

One study made this comparison (Mindel 1986; n = 60). It reported median values. Sixty women were treated with either oral acyclovir for 42 days or oral acyclovir for five days followed by placebo for 37 days.

Primary outcomes

3.1.1 Duration of symptoms from onset of treatment

There was no significant difference between the groups in duration of symptoms (Table 9).

3.1.2 Time to first recurrence

The median time to first recurrence in the long course group was 66.5 days, and 24 days in the short course group (P < 0.0001). However the study authors reported that the difference between the groups was only significant during the treatment period (42 days) and not for longer follow-up.

3.1.3 Adverse events

There was no difference between the groups in the rate of adverse events, which were uncommon in both groups. Reported events included constipation, diarrhoea, and bilirubin elevation. See Analysis 9.1.

Secondary outcomes

3.1.4 Duration of lesions from onset of treatment

There was no significant difference between the groups in duration of lesions (Table 9).

Our other secondary outcomes were not reported.

3.2 High dose versus standard dose acyclovir

One study made this comparison (Wald 1994; n = 56). It reported median values. Participants were treated with either oral acyclovir 1 gm daily or 4 gm daily for five days.

Primary outcomes

3.2.1 Duration of symptoms from onset of treatment

There was no significant difference between the groups in duration of symptoms. See Table 10.

3.2.2 Time to first recurrence

There was no significant difference between the groups in time to first recurrence. See Table 10.

3.2.3 Adverse events

There was no statistically significant difference between the groups in the rate of adverse events (RR 7.08, 95% CI 0.41 to 121.05), but all reported events occurred in the intervention group (gastric disturbance in seven participants and headache in two participants). See Analysis 9.2.

Secondary outcomes

3.2.4 Duration of lesions from onset of treatment

There was no significant difference between the groups in duration of lesions. See Table 10.

Our other secondary outcomes were not reported.

3.3 High dose versus standard dose famciclovir

One study looked at different dosing regimens of famciclovir (Niimura 1996).

Primary outcomes

3.3.1 Duration of symptoms from onset of treatment

There was no significant difference between the groups in duration of symptoms. See Analysis 13.1.

3.3.2 Time to first recurrence

There were no studies that looked at this outcome.

3.3.3 Adverse events

There were no studies that looked at this outcome.

Secondary outcomes

3.3.4 Duration of lesions from onset of treatment

There was no significant difference between the groups in visibility of lesions at day 5. See Analysis 13.2.

No other secondary outcomes were reported.

4 Antiviral versus interferon

4.1 Topical acyclovir versus intramuscular interferon

One study with 105 participants made this comparison (Levin 1989).

Primary outcomes

4.1.1 Duration of symptoms from onset of treatment

There was no difference between the groups in symptom duration (MD 1.03 days, 95% CI -0.85 to 2.91; 1 RCT, 105 participants; Analysis 10.1).

4.1.2 Time to first recurrence

This outcome was not reported.

4.1.3 Adverse events

Compared to the topical acyclovir group, the intramuscular interferon group reported higher rates of visual disturbances (RR 2.76, 95% CI 1.23 to 6.19), dizziness (RR 6.83, 95% CI 1.59 to 29.25), nausea (RR 1.81, 95% 1.10 to 2.96), anorexia (RR 1.74, 95% CI 1.10 to 2.75), sweating (RR 19.31, 95% CI 1.14 to 327.34), fever (RR 3.82, 95% CI 2.36 to 6.18), fatigue (RR 1.44, 95% CI 1.09 to 1.90), chills (RR 3.13, 95% CI 1.99 to 4.91), headache (RR 1.57, 95% CI 1.14 to 2.17), myalgia (RR 1.74, 95% CI 1.30 to 2.34), and neutropenia (RR 5.69, 95% CI 2.33 to 13.90). There was no difference between the groups in rates of diarrhoea or vomiting (Analysis 10.2).

Secondary outcomes

4.1.4 Duration of lesions from onset of treatment

There was no difference between the groups in lesion duration (MD 1.58, 95% CI -0.38 to 3.54; 1 RCT, 105 participants; Analysis 10.3).

Our other secondary outcomes were not reported.

5 Interferon versus placebo

5.1 Topical interferon cream versus placebo

Batcheler 1986 reported this comparison. Only females (n = 36) were included in this study. Data were unsuitable for analysis as no standard errors were reported.

Primary outcomes

5.1.1 Duration of symptoms from onset of treatment

This outcome was reported for only 30 (83%) of the participants. The authors stated that there was no significant difference between the groups. See Table 11.

5.1.2 Time to first recurrence

This outcome was not reported.

5.1.3 Adverse events

The authors reported that there were no adverse events in either study arm.

Secondary outcomes

5.1.4 Duration of lesions from onset of treatment

The authors stated that there was no significant difference between the groups (see Table 11).

Our other secondary outcomes were not reported.

5.2 Subcutaneous interferon versus placebo

One study reported this comparison (Mendelson 1986). It included 31 participants.

Primary outcomes

5.2.1 Duration of symptoms from onset of treatment

The authors stated that there was no significant difference between the groups (Analysis 11.1).

5.2.2 Time to first recurrence

The authors stated that there was no difference between the groups in time to first recurrence, but no numerical data were presented for this outcome.

5.2.3 Adverse effects

Compared to the placebo group, the subcutaneous interferon group reported higher rates of fever (RR 12.86, 95% CI 1.91 to 86.44), headache (RR 3.57, 95% CI 1.23 to 10.36), chills (RR 5.89, 95% CI 1.58 to 22.03), anorexia (RR 8.57. 95% CI 1.22 to 60.07), and neutropenia (RR 29.00, 95% CI 1.90 to 443.25). There was no difference between the groups in rates of myalgia, nausea, vomiting, fatigue, and diarrhoea (see Analysis 11.2).

Secondary outcomes

5.2.4 Duration of lesions from onset of treatment

The authors stated that there was no significant difference between the groups (Analysis 11.3).

Our other secondary outcomes were not reported.

5.3 Intramuscular interferon versus placebo

One study reported this comparison (Pazin 1987). The study included 69 participants, all women.

Primary outcomes

5.3.1 Duration of symptoms from onset of treatment

Data were reported in graphical form. The study authors reported that although the mean duration of pain in the intervention group was consistently two days shorter than in the placebo group, the difference was not significant.

5.3.2 Time to first recurrence

The study authors stated that life table analysis showed no difference between the groups in time to first recurrence. Eighty per cent of participants were followed for at least 230 days.

5.3.3 Adverse events

Compared to the placebo group, the interferon group had increased rates of transient neutropenia (RR 23.91, 95% CI 1.48 to 385.85; 1 RCT, n = 64) and thrombocytopenia (RR 11.51, 95% CI 0.68 to 196.20). See Analysis 12.1.

Secondary outcomes

5.3.4 Duration of lesions from onset of treatment

The study authors stated that there was no significant difference between the groups in duration of lesions. See Table 12.

Our other secondary outcomes were not reported.

6 Natural products

There were no included studies that looked at this comparison.

Sensitivity Analysis

It was not possible to conduct a sensitivity analysis by excluding studies at high risk of bias, as the included studies did not differ substantially with respect to risk of bias. Nearly all studies were at unclear risk of bias in most domains. Use of a random-effects model did not change the statistical significance of any of the findings, with the exception of the female subgroup in Analysis 1.1; Figure 4.

DISCUSSION

Summary of main results

See Summary of findings for the main comparison, Summary of findings 2.

There were four randomised controlled studies that compared oral acyclovir with placebo for first-episode genital herpes. The dose of acyclovir was 200 mg given five times daily for either 5, 7, or 10 days. The pooled data from two studies showed that symptom duration, including lesion duration, was significantly shorter in the acyclovir group (mean difference (MD) -3.3 days, 95% CI -4.94 to -1.46). There was no difference in time to first recurrence. Few adverse effects were reported. One study that compared short duration (5 days) with longer duration (42 days) acyclovir found no difference in symptom duration. Similarly, high dose acyclovir (4 gm x 4 days) did not show any difference in symptom duration compared to standard dose (1 gm x 4 days). The two studies that compared oral acyclovir (200 mg x 5 daily) with oral valaciclovir (300 mg or 500 mg x 2 daily) found no difference in symptom duration. One study of varying regimes of famciclovir (125 mg, 250 mg, or 500 mg X 3 daily) also found no difference in symptom duration. Of the three studies comparing intravenous acyclovir with placebo, two reported shorter median symptom duration and all three a shorter median duration of lesions. Four studies compared topical acyclovir with placebo. Pooled data from three studies showed no difference in symptom duration.

Placebo controlled studies of other antivirals such as cicloxolone, carbenoxolone, adenosine arabinoside, idoxuridine, and tromantadine were either too small or had such poor reporting of study methods to enable any meaningful conclusions. The one study comparing oral acyclovir with inosine prabonex found no overall difference in symptom duration or time to first recurrence, however the duration of lesions was shorter for the acyclovir group. When topical acycylovir, not shown to be beneficial in the previous randomised placebo-controlled studies, was compared to interferon, in one study, there was no difference in symptom duration. The authors of a study comparing topical interferon cream with placebo reported no difference in symptom duration. Similarly, two studies comparing subcutaneous interferon or intramuscular interferon with placebo also found no benefit. One study of topical proflavine with light exposure and another of the antibiotic, co-trimoxazole also showed no benefit when compared with placebo.

Overall completeness and applicability of evidence

Many of the included studies in this review were old with data reporting median values that precluded us from being able to pool the data. In addition, the age of the studies also meant that when data were missing, we were unable to obtain additional information. There were no studies comparing either valaciclovir or famciclovir with placebo and no studies comparing famciclovir with acyclovir. We were also lacking studies comparing imiquimod to placebo, no treatment or other medications and studies looking at the use of natural products.

None of the included studies contained pregnant women as part of the participant group. For this reason we were unable to assess the effects of these medications on outcomes looking at neonatal effects and rates of caesarean section delivery. In addition, for the primary outcome of time to first recurrence the available data was limited and not presented in the appropriate form to allow meta-analysis.

Few studies with acyclovir had antibody levels and so we were unable to confirm that this was a first episode of primary infection. In the one study where this information was available, symptom duration appeared to be reduced only for those with a first episode of primary infection. Whether gender affects the efficacy of acyclovir for symptom duration is not clear due to small sample sizes.

Our intention was to perform subgroup analyses on the following variables gender, length of treatment, type of drug within a class, duration of time between appearance of lesions and initiation of treatment, immunodeficiency and first episode of primary infection versus first episode of non-primary infection. The was insufficient data to explore the majority of these subgroups and those subgroups we were able to present (gender and first episode of primary infection vs first episode of non primary infection) only contained a limited number of small studies.

Quality of the evidence

We judged most of the studies at unclear risk of bias in most domains. This is in large due to the age of the included studies and the brief reporting of the methods in the included studies. This does not necessarily imply that the studies were of poor quality, but rather that we did not have the information that we required to be able to classify these studies as either low or high risk. In addition to the unclear risk of bias information, there were very few studies that we were able to include in the meta-analysis. Because of the low number of studies that were able to inform the meta-analysis the confidence intervals were relatively wide and so for this reason we downgraded the level of evidence for reasons of imprecision. This, in combination with some apparent heterogeneity, led us to grade most of the evidence as low.

Potential biases in the review process

As some of these trials were carried out before there was an international requirement for trial registration, it is possible that some studies may have been missed. However, we were unable to construct a funnel plot to assess publication bias, as there were fewer than 10 studies in any analysis.

Agreements and disagreements with other studies or reviews

Other reviews state that antiviral therapy with oral acyclovir, its prodrug valacyclovir, or with famciclovir, is effective in treating first-episode genital herpes. All three drugs were found to be equipotent; however, acyclovir is less well absorbed and requires a more frequent dosing schedule. There is agreement that topical antivirals have limited effectiveness (Leung 2000; Patel 2002). The only indication for the use of intravenous therapy is when the patient is unable to swallow or tolerate oral medication. None of these treatments influence subsequent recurrence. All of the studies in this review used acyclovir 200 mg five times daily for either 5, 7, or 10 days. However, current guidelines also recommend 400 mg three times a day for seven days (CDC 2015) or five days (IUSTI 2010). These guidelines recommend that treatment should be commenced within five days of the start of the episode or while new lesions are still forming.

AUTHORS' CONCLUSIONS

Implications for practice

There is support in this review for the current recommended treatment of symptomatic first episode genital herpes with oral acyclovir. The evidence presented here is graded as low quality but this is in part due to the poor reporting of the included studies. Most of these studies are from the 1980s and at this time the brief way studies were reported does not allow us to adequately judge the quality of the included studies.

Low quality evidence did not support the use of topical acyclovir as an effective treatment for genital herpes.

We did not find sufficient evidence for many of the possible treatments of first episode herpes nor were we able to assess which was the most advantageous dosage for the treatments looked at within this review.

Implications for research

There were no studies which looked at immunocompetent individuals or pregnant women. We would like to see research done in this area to determine the most advantageous treatment and regimen for these particularly vulnerable groups to reduce the significant morbidity and mortality associated with them. Asymptomatic disease probably leads to most cases of transmission, so, the role for antivirals in reducing transmission needs ongoing research.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adams 1976

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of patients randomised: unknown Number of patients analysed: 49 (27 women, 22 men) Number of withdrawals/exclusions: unclear as done on the basis of episodes (of the 74 episodes of genital herpetic infection in men, 63 episodes in 55 men were evaluable according to the criteria outlined above. 3 patients were excluded because *Herpesvirus hominis* was not recovered from the genital lesions, and 8 were excluded because they did not return after the 3-day visit. Of the 77 episodes in women, 17 were excluded because the woman was not using reliable contraception. 10 of these 17 women had cultures positive for *Herpesvirus hominis* and were followed without therapy as described above. Of the remaining 60 episodes in women, 13 were excluded because *Herpesvirus hominis* was not recovered, and follow-up study was not possible in 2 other cases) Sources of funding: this research was supported by research grant no. AI-12192 and institutional research fellowship award no. AI-00191 from the National Institute of Allergy and Infectious Diseases, and by a grant from Parke, Davis and Company
Participants	Setting: Harborview Venereal Disease Clinic, Seattle **Inclusion criteria**: new lesions formed within 2 days of entry into study, women using reliable contraception (however, if not using reliable contraception, still followed with no treatment) **Exclusion criteria**: pregnant, herpes virus not recovered from lesions, failure to complete protocol Type of first-episode herpes: unknown
Interventions	(1) 3% ara-A (adenosine arabinoside) in petroleum ointment base: topical application to each lesion 4 x daily for 7 days (then after 45% of women had entered the study, 6 women were assigned to treatment with 3% ara-A in water-soluble gel to be applied 4 times daily to external lesions together with 5 ml to be instilled twice daily intravaginally) (2) Indistinguishable petrolatum ointment placebo: topical application to each lesion 4 x daily for 7 days (then after 45% of women had entered the study, 3 women were assigned to treatment with placebo water-soluble gel to be applied 4 times daily to external lesions together with 5 ml to be instilled twice daily intravaginally) (3) No treatment
Outcomes	Mean total number of lesions (before treatment and at end of treatment), mean duration (days) of lesions (after treatment and total), mean duration (days) of pain (after treatment and total), mean duration (days) of viral shedding (after treatment and total), recurrence during follow-up

Adams 1976 *(Continued)*

Possible conflicts of interest	
Notes	Data is available in raw form. Application for women was changed during study from topical ointment to gel that was topically and intravaginally applied. Brief results on women with topical versus intravaginal and topical application. More information would be needed for analysis however, as paper is from 1976; we are not expecting to be able to receive this. Have emailed: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"…to treatment with an indistinguishable placebo gel administered according to the same schedule, or to no therapy. Thus ara-A or placebo ointment or gel were given in a double-blind fashion"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear how many first-episode participants randomised. Overall 15% of male and 40% of female episodes not included in analysis: unclear how many participants this involved and whether they were first-episode or not, as study also included participants with recurrent disease
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Potential bias due to change of intervention during study

Altomare 1985

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of patients randomised: unknown Number of patients analysed: 21 first-episode (40 altogether) Sex: 14 male, 7 female Age: mean age overall 37.5 +/- 12.3 years Number of withdrawals/exclusions: 3 people from the placebo group were considered as dropouts because they did not report to the outcome assessor Sources of funding: not reported
Participants	Setting: Milano Italy, Institute of Clinical Dermatology

Altomare 1985 *(Continued)*

	Inclusion criteria: patients with clinical symptoms of GH not more than 2 days (first-episode and recurrent episode included) **Exclusion criteria**: patients less than 16 years old, pregnant or lactating women, people using topical corticosteroids or general cytostatics, immunosuppressants or other drugs that would interfere with the activity of the treatment. Also excluded patients who could not tolerate the treatment, patients with edematous lesions, and patients who were on a systemic treatment for other diseases Type of first-episode herpes: unknown
Interventions	Group 1: tromantadine applied with a light massage 5 times per day for men and 2 times for women who reapplied after washing. All patients had to disinfect their hands after application Group 2: placebo Duration of treatment: 12 days In the case of intravaginal manifestations, investigators provided 3 cc of an 'ointment' applied with a special applicator 2 times a day in the first 4 days, and 1 time for the following days
Outcomes	Proportion healed at 3, 6, 9, and 12 days: this included the disappearance of objective and subjective symptoms: lesions, oedema, burning, pain, itching, 'sense of tension on lesion', dysuria; and complete re-epithelisation and no new lesion Side effects
Possible conflicts of interest	Unknown
Notes	Translated by Nancy Santoressi

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a randomised list
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The treatment and the placebo were absolutely indistinguishable in appearance, consistency, colour
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind, and notes that one doctor performed outcome assessment, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 people from the placebo group were considered as dropouts because they did not report to the outcome assessor - unclear whether these people had first-episode or recurrent disease (thus up to 15% of relevant data could be missing)
Selective reporting (reporting bias)	Unclear risk	All outcomes seem to be reported but data for first-episode only reported separately for one outcome and only reported for those who healed within 12 days

Altomare 1985 *(Continued)*

Other bias	Unclear risk	Insufficient details about which participants received ointment prescribed for intravaginal manifestations

Batcheler 1986

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of patients randomised: 111 (first episode of primary infection and first episode of non-primary) Number of patients analysed: 77 (first episode of primary infection and first episode of non-primary), 36 (primary) (1 excluded from final analysis as patient required hospitalisation as attack was so severe) Number of withdrawals/exclusions: 34 (9 due to no follow-up, 1 due to pregnancy, 16 due to non-herpetic condition, 8 with uncertain diagnosis) Sources of funding: not specified
Participants	Setting: patients were informed female volunteers referred to National Women's Hospital, Auckland, by local doctors and Family Planning Association clinics **Inclusion criteria**: women with diagnosis of GH **Exclusion criteria**: pregnancy, serious coexisting medical problems or drug allergies Age: (1) Treatment - 22.4 years (mean) (first-episode GH) (2) Placebo - 24.1 years (mean) Sex: all female Ethnicity: (1) Treatment - 15 Caucasion, 1 Māori (2) Placebo - 18 Caucasion, 1 Māori Type of first-episode herpes: primary and non-primary
Interventions	(1) Treatment: refrigerated cream containing beta-interferon (20,000 iu/g) applied topically to lesions 5 to 6 x daily until lesion healing (2) Placebo: refrigerated placebo cream applied topically to lesions 5 to 6 x daily until lesion healing
Outcomes	Duration of symptoms before treatment, duration of pain, duration of discharge, duration of itch, duration of dysuria, time until crusting, time until healing, length of viral shedding
Possible conflicts of interest	
Notes	Have emailed for details regarding randomisation, allocation, blinding, and outcome assessment: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Cream allocation was done in a random double-blind way"

Batcheler 1986 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Patients were then assigned either cream containing beta-Interferon (20,000 iu/g) or placebo cream. Cream allocation was done in a random double-blind way." No details as to appearance of placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient had a particularly severe attack, requiring hospitalisation for a month. As she was so much worse than all other patients she was excluded from the final analysis" 35/36 (> 97%) included in analysis
Selective reporting (reporting bias)	Unclear risk	Table seems to have reported all possible outcomes, but no protocol available
Other bias	Low risk	No other potential bias identified

Bryson 1983

Methods	Randomised, placebo-controlled, parallel trial Unit of allocation: individuals Number of patients randomised: 68 (52 with HSV-1 infection) Number of patients analysed: 48 Number of withdrawals/exclusions: 6 (3 participants dropped out of the study, and 3 participants with vesicular and ulcerative lesions did not have initially positive cultures for HSV) Sources of funding: not specified
Participants	Setting: University Centre for Infectious Diseases clinic at the University of California in Los Angeles, United States of America **Inclusion criteria**: first episode of GH **Exclusion criteria**: prior history of vesicular or ulcerative genital lesions, lesions present for more than 6 days, pregnant or nursing women, underlying diseases, inadequate contraception, patients who had tried to obtain some form of antiviral treatment within one week before entry, initial negative cultures to HSV Age: (1) Acyclovir: 25 (mean) (2) Placebo: 25 (mean) Sex: (1) Male: 7, female: 16 (2) Male: 10, female: 15 Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: 200 mg acyclovir capsule taken orally for 10 days, 5 x a day (2) Placebo: placebo capsule taken orally for 10 days, 5 x a day

Bryson 1983 *(Continued)*

Outcomes	Time to healing, duration of shedding, time to crusting, duration of symptoms, severity of symptoms
Possible conflicts of interest	An author is from Burroughs Wellcome Company. Dr Anthony Segretti from Burroughs Wellcome Company was used for statistical consultation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomised". Emailed regarding details of randomisation: no response
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" in title, no other mention elsewhere. Emailed regarding details of blinding: no response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	High risk	"Three subjects dropped out of the study, and three subjects with vesicular and ulcerative lesions did not have initially positive cultures for herpes simplex virus. Data from these six patients are not included in the analysis." *"Of the 68 patients who were entered into the original study (40 females, 28 males)…. 63 were available for follow-up. There were 52 subjects with HSV 2 infections".* Not stated which groups the 11 missing subjects were in, and not stated why the non-HSV-2 participants were excluded
Selective reporting (reporting bias)	High risk	As above – no explanation why HSV-1 appears to have been excluded from follow-up
Other bias	Low risk	No other potential bias identified

Corey 1982a

Methods	Randomised, parallel multicentre trial Unit of allocation: individuals Number of patients randomised: 94 (patients with first-episode GH) Number of patients analysed: 77 Number of withdrawals/exclusions: 17 (14 were excluded from the analysis because HSV was not isolated from their external genital lesions before therapy, 3 were excluded because they did not attend follow-up visits frequently enough to permit evaluation of the effect of therapy of the duration of viral shedding or lesion healing) Sources of funding: Burroughs Wellcome Company and National Institutes of Health

Corey 1982a *(Continued)*

Participants	Setting: University of Washington Genital Herpes Simplex Virus Clinic located at the Harborview Medical Centre, Seattle, Washington, and at the Emory University and the De-Kalb County Health Department in Atlanta, Georgia, United Stated of America **Inclusion criteri**a: initial or recurrent GH, presented within 6 days of onset of lesions if first-episode, and within 48 hours if recurrent, patients in good health **Exclusion criteria**: HSV not isolated from their external genital lesions before therapy, pregnancy, and if receiving any form of immunosuppressive therapy Age: 27 years (mean) - of participants with first-episode GH Sex: (1) first episode primary acyclovir - 8 males, 18 females first episode non-primary acyclovir - 4 males, 8 females (2) First episode of primary infection placebo - 6 males, 17 females First episode of Non-primary placebo - 7 males, 9 females Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: 5% acyclovir in polyethylene glycol ointment for 7 days, 4 x a day (every 4 hours while awake) (2) Placebo: polyethylene glycol ointment alone for 7 days, 4 x a day (every 4 hours while awake)
Outcomes	Pain, viral shedding, time to healing, time to crusting, recurrence
Possible conflicts of interest	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Separate randomisation codes were generated for each study centre, for patients with first episodes and those with recurrent episodes, and for male and female patients”. Emailed regarding details of allocation process: received response, however, was not specific enough to be considered low risk
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Packaged in identically coded 15g tubes”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Ninety four patients with first episodes of infection were enrolled. Fourteen were excluded from analysis because HSV was not isolated from their external genital lesions before therapy and three were excluded because they did not attend follow-up visits frequently enough to permit evaluation of the effect of therapy of the duration of viral shedding or lesion healing”

Corey 1982a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Corey 1982b

Methods	Randomised, parallel trial Unit of allocation: individuals Number of patients randomised: 89 Number of patients analysed: 69 Number of withdrawals/exclusions: 13 (7 drug, 6 placebo) did not comply with the study protocol, 13 (7 drug, 6 placebo) did not comply with the study protocol Sources of funding: Burroughs Wellcome Company and National Institutes of Health
Participants	Setting: Between April 1979 and August 1980, patients referred to the University of Washington Genital Herpes Simplex Virus clinic located Harbourview Medical Center, Seattle, Washington, United States of America **Inclusion criteria**: episode of GH, initial or recurrent **Exclusion criteria**: presentation with symptoms that have been present for more than 6 days (for first-episode) or over 48 hrs (recurrent) Age: 25.7 years (mean) - of participants with first-episode GH Sex: 64% female - of participants with first-episode GH Ethnicity: 97% Caucasian - of participants with first-episode GH Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: 5% acyclovir in polyethylene glycol ointment for 7 days, 4 x a day or 6 x daily if after Jan 1980 (2) Placebo: polyethylene glycol ointment for 7 days, 4 x a day or 6x daily if after Jan 1980
Outcomes	Mean duration of time from the onset of lesions until initiation of therapy, mean number of lesions, mean lesion area, itching, pain, dysuria, vaginal discharge, viral shedding from lesions, time to crusting of lesions, duration of lesions
Possible conflicts of interest	Ronald E Keeney and L Gray Davis are from Burroughs Wellcome Company
Notes	Ointment was applied 6 x a day after Jan 1980

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were then randomly assigned". Emailed regarding details of allocation process: received response however was not specific enough to be considered low risk "block randomisation"

Corey 1982b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"In a double-blind fashion". Emailed response: "placebo was identical"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT. No information on withdrawals
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Corey 1983

Methods	Randomised, placebo-controlled, parallel trial Unit of allocation: individuals Number of patients randomised: 32 Number of patients analysed: 31 Number of withdrawals/exclusions: 1 (HSV was never isolated during the study period, and because acute and convalescent sera showed unchanging high titres of HSV-2 neutralising antibody, suggesting past asymptomatic HSV-2 infection) Sources of funding: Burroughs Wellcome Company and National Institutes of Health
Participants	Setting: Harborview Medical Center Genital Herpes Clinic and at the Clinical Research Centre, University Hospital, Seattle, Washington, United States of America **Inclusion criteria**: no previous history of either oral-labial or GH simplex infection, presented within 7 days of onset of symptoms, extensive genital lesions or systemic symptoms, not pregnant, not receiving any form of immunosuppressive therapy, in general good health Sex: (1) Acyclovir - 1 male, 14 females (all first-episode GH) (2) Placebo - 3 males, 13 females (1) Acyclovir - 1 male, 13 females (primary first-episode GH) (2) Placebo - 2 males, 11 females Age: Mean age of all patients was 26 years (nil else stated) Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: 5 mg/kg intravenous for 5 days (15 doses), every 8 hours over 1 hour (2) Placebo: normal saline intravenous for 5 days (15 doses), every 8 hours over 1 hour

Corey 1983 *(Continued)*

Outcomes	Complete healing of genital lesions, subsequent recurrence rates, viral shedding, complete crusting of genital lesions, pain, itching, vaginal discharge, dysuria (women only), sore throat, constitutional symptoms, toxicity, time to first recurrence
Possible conflicts of interest	People from Burroughs Wellcome Company helped develop the protocol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Patients were randomly assigned”. Emailed regarding details of allocation process: received response, however, was not specific enough to be considered low risk
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Emailed for information: "IV solutions were administered by a study nurse; all the solutions were made up in a research pharmacy and the bags were identical"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient was excluded from all analyses because herpes simplex virus was never isolated during the study period and serology showed high titres of HSV 2 neutralising antibody suggesting past asymptomatic HSV 2 infection"
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Csonka 1984

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of patients randomised: 79 (19 with initial GH) Number of patients analysed: 11 (initial GH) Number of withdrawals/exclusions: 22 (10 participants were excluded from the analysis due to late entry or inadequate viral confirmation, one patient was excluded because of misdiagnosis, and 11 participants defaulted) Sources of funding: Dr FR House of Guy's Hospital Medical School for the statistical analyses, Mrs Ruth Parry for technical assistance, Biorex Laboratories for the supply of materials for the trial and for the in vitro study, and Dr P Thornton for his help with the preparation of the paper
Participants	Setting: attended Praed Street Clinic of St Mary’s Hospital, London

Csonka 1984 *(Continued)*

	Inclusion criteria: presented within 48 hours of the onset of a recurrent attack or within 5 days of an initial attack, over 16 years, no other clinically obvious genital infection, had not received antiviral treatment within the previous 14 days **Exclusion criteria**: late entry or inadequate viral confirmation, misdiagnosis, patient defaulting Sex: (1) Carbenoxolone: male – 3, female – 3 (initial GH before exclusions) (2) Cicloxolone: male – 4, female – 3 (3) Placebo: male – 2, female - 4 Type of first-episode herpes: not specified
Interventions	(1) Carbenoxolone: 2% carbenoxolone sodium cream applied sparingly to the lesions 5 x daily for 7 days or for the duration of the lesions and for 24 hours after healing, whichever was the shorter period (2) Cicloxolone: 2% cicloxolone sodium cream applied sparingly to the lesions 5 x daily for 7 days or for the duration of the lesions and for 24 hours after healing, whichever was the shorter period (3) Placebo: control cream of the same formula (but containing neither test medication) applied sparingly to the lesions 5 x daily for 7 days or for the duration of the lesions and for 24 hours after healing, whichever was the shorter period
Outcomes	Free of symptoms at the end of 5 days, free of symptoms at the end of treatment, free of lesions at the end of 5 days, free of lesions at the end of treatment, side effects
Possible conflicts of interest	Unknown
Notes	Data are in dichotomous form. Have emailed for raw data and allocation/randomisation/blinding details: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“randomised”
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The creams were dispensed in numbered 15 g tubes"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	High risk	"Ten patients were excluded from the analysis due to late entry or inadequate viral confirmation, one patient was excluded because of misdiagnosis, and 11 patients defaulted." Only 11/19 (57%) participants included in analysis and text suggests that there are other "defaulters" not included in analysis
Selective reporting (reporting bias)	Unclear risk	No information provided

Csonka 1984 *(Continued)*

Other bias	Low risk	No other potential bias identified

Fiddian 1983

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 107 (first-episode) Number of participants analysed: 101 Number of withdrawals/exclusions: 6 (4 in the placebo group and 2 in the acyclovir group failed to return to the clinic for follow-up visits) Sources of funding: not mentioned
Participants	Setting: various S.T.D. clinics of the participating centres, United Kingdom **Inclusion criteria**: presented within 5 days of onset of lesions if initial, and within 24 hours if recurrent, male participants and females adequately protected from pregnancy, aged 16 years or more, who had not received other specific antiviral therapy in the preceding 14 days, not having other infections that might interfere with the assessments **Exclusion criteria**: none stated Age: (1) Acyclovir: 25.5 years (mean) (2) Placebo: 24.5 years (mean) (participants with first-episode GH) Sex: (1) Acyclovir: male - 19, female - 35 (2) Placebo: male - 16, female - 31 Type of first-episode herpes: unknown
Interventions	(1) Acyclovir: 30 g tube of 5% acyclovir in an aqueous cream base containing propylene glycol applied liberally for 10 days or until healing has occurred, 5 x a day (2) Placebo: 30 g tube of aqueous cream base alone applied liberally for 10 days or until healing has occurred, 5 x a day
Outcomes	Viral shedding, pain, itching, dysuria, discharge, combined symptoms, healing time of all sites, healing time of original external lesions, adverse events
Possible conflicts of interest	Author AP Fiddian is from Wellcome Research Laboratories, which may be the company producing the drug of interest
Notes	Data is in median form. Emailed to try and obtain data in raw form: our message was forwarded to Wellcome and GSK and they had no information to provide It appears that subgroups of participants in this study are reported in separate publications by some of the co-authors (see Kinghorn 1983 and Thin 1983, referenced as co-publications of Fiddian 1983), though this is not clearly reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Fiddian 1983 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Male and female patients were randomly allocated separately to the treatment groups." Emailed regarding details of randomisation: no information able to be provided
Allocation concealment (selection bias)	Unclear risk	"Male and female patients were randomly allocated separately to the treatment groups under double-blind conditions"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Male and female patients were randomly allocated separately to the treatment groups under double-blind conditions." Emailed regarding details of blinding: no information able to be provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Four patients in the placebo group and two in the acyclovir group failed to return to the clinic for any follow-up visits and so have had to be excluded from the analysis of the results"
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Fife 1997

Methods	Randomised, double-blind, parallel trial Unit of allocation: individuals Number of participants randomised: 643 Number of participants analysed: 643 (114 had primary disease) Number of withdrawals/exclusions: 70 (13 valaciclovir and 11 acyclovir had antibodies to both HSV-1 and HSV-2 at enrolment, they may have unrecognised first episodes - they were included in the analysis as non-primary cases, exclusion of these participants did not affect the results, 25 valaciclovir and 21 acyclovir failed to take at least 80% of study medication - these participants were included in the ITT and safe analysis) Sources of funding: Glaxo Wellcome Inc
Participants	Setting: Recruited from 54 sites in the United States, UK, and Australia. Most were student health clinics, STD clinics or family planning clinics **Inclusion criteria**: no prior history of GH, diagnosis with first-episode genital HSV infection, > 18 years old, otherwise healthy, presented for enrolment within 72 hours of lesion onset **Exclusion criteria**: pregnant or nursing, HIV positive Age: (1) Acyclovir group: 23 years (median) (2) Valaciclovir group: 23 years (median) Sex: (1) Acyclovir group: female - 208, male - 112 (2) Valaciclovir group: female - 207, male 116

Fife 1997 *(Continued)*

	Type of first-episode herpes: primary and non-primary
Interventions	1) Acyclovir group: oral 5 capsules with 200 mg acyclovir and 4 tablets of placebo daily with for 10 days, 5 x daily (200 mg) (2) Valaciclovir group: Oral 5 capsules of placebo and 4 tablets daily with 500 mg valaciclovir for 10 days, twice daily (1000 mg)
Outcomes	Duration of viral shedding, duration of pain, time to resolution of all symptoms, time to healing - ITT, time to healing - HSV proven
Possible conflicts of interest	Some authors from the Valaciclovir International Herpes Simplex Virus Study Group are from Glaxo Wellcome Inc
Notes	Says participants were assigned "drug or matching placebo" however, cannot see information on a placebo group. Emailed for more information: "All subjects received one of the active treatments. All participants received a total of five capsules and 4 tablets each day. The tablets contained either 500 mg of valaciclovir or were matching placebos, while the capsules contained 200 mg of acyclovir or were matching placebos" No totals were provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Subjects were then randomised (1:1)”
Allocation concealment (selection bias)	Unclear risk	Email response: “Both the patients and the clinical evaluation team were masked to treatment assignment”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Email response: "Both the patients and the clinical evaluation team were masked to treatment assignment”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both the participants and the clinical evaluation team were masked to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	“All 643 patients were included in the intent-to-treat analysis of primary efficacy endpoints and in the evaluation of safety”
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Kinghorn 1986a

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 50

Kinghorn 1986a *(Continued)*

	Number of participants analysed: 49 Number of withdrawals/exclusions: 1 (patient defaulted before completing the protocol and was excluded from the analysis) Sources of funding: not mentioned
Participants	Setting: patients presenting to the department of genitourinary medicine, Royal Hallamshire Hospital, Sheffield, England, United Kingdom **Inclusion criteria**: men and women aged 16 years or more who presented within 6 days of the onset of symptoms of first-episode GH **Exclusion criteria**: patients were excluded if they had used other antiviral or immune stimulation treatment within the preceding seven days, if they had underlying immune deficiency, hepatic or renal disease, or were women who were not using a valid form of contraception Age: (1) Acyclovir cream: 21.5 years (mean) (2) Placebo cream: 20.7 years (mean) Sex: (1) Acyclovir cream: male - 7, female - 17 (2) Placebo cream: male - 7, female - 18 Type of first-episode herpes: primary and non-primary (have not analysed separately)
Interventions	(1) Acyclovir cream: 5% acyclovir cream applied topically 5 x a day for 7 days (2) Placebo cream: matching placebo cream applied topically 5 x a day for 7 days All participants were treated with oral acyclovir 200 mg 4 x daily for 7 days
Outcomes	Mean (SD) duration of symptoms (days): itching, pain, dysuria, discharge, all symptoms; mean (SD) duration (days) of viral shedding: external lesions, urethra or cervix; mean (SD) time (days) to healing: original external lesions, all lesions; recurrence; adverse events
Possible conflicts of interest	D Jones and E Hickmott are from Clinical and Applied Research Division, Wellcome Research Laboratories, Beckenham, Kent – the company that may have funded and supplied intervention
Notes	Treatment within 6 days of presentation of symptoms. Have emailed the author for more information on the allocation process and blinding, and also for more time to first recurrence data: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“...they were given topical treatment with either 5% acyclovir cream or a matching placebo cream. Patients in both treatment groups were given identical advice regarding additional symptomatic treatment.” “The treatment was dispensed in a double-blind fashion"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given

Kinghorn 1986a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of 50 patients who entered the study one defaulted before completing the protocol and was excluded from the analysis"
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Unclear whether data are a subset of Fiddian 1983

Kinghorn 1986b

Methods	Randomised, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 40 Number of participants analysed: 38 Number of withdrawals/exclusions: 2 (were withdrawn from analysis because they failed to comply with the protocol) Sources of funding: Wellcome Foundation
Participants	Setting: patients presenting to the department of genitourinary medicine, Sheffield, England, United Kingdom **Inclusion criteria**: presented within 6 days of onset of symptoms **Exclusion criteria**: used other antiviral or immune stimulation treatment within the preceding 7 days, underlying immune deficiency, hepatic or renal disease, inadequate contraception Age: (1) Acyclovir: 23.2 years (mean), 1.18 SEM (2) Placebo: 23.3 years (mean), 1.15 SEM (3) Co-trimoxazole: 23.4 years (mean), 1.31 SEM (4) No co-trimoxazole: 23.4 (mean), 1.02 SEM Sex: (1) Acyclovir: male - 9, female - 10 (2) Placebo: male - 9, female - 10 (3) Co-trimoxazole: male - 10, female - 8 (4) No co-trimoxazole: male - 8, female - 12 Type of first-episode herpes: primary and non-primary (have not analysed separately)
Interventions	(1) Acyclovir: 200 mg acyclovir tablets taken orally 5 x daily for 7 days (2) Placebo: placebo tablets identical to acyclovir tablets taken orally 5 x daily for 7 days (3) Acyclovir tablets + co-trimoxazole tablets: 200 mg acyclovir tablets + 160 mg trimethoprim and 800 mg sulphamethoxazole taken orally (acyclovir 5 x a day, co-trimoxazole 2 x daily) for 7 days (4) Placebo acyclovir and co-trimoxazole tablets: placebo identical to acyclovir tablets and then co-trimoxazole tablets taken orally (placebo identical to acyclovir tab 5 x a day and co-trimoxazole tablet 2 x daily) for 7 days

Kinghorn 1986b *(Continued)*

Outcomes	Mean (SD) duration (days) of: viral shedding, pain, all symptoms; mean (SD) time to healing (days) of: original external lesions, all lesions; recurrences; adverse events
Possible conflicts of interest	Al-Hasani G, CW Potter and E Hickmott are all from Wellcome Research Labs
Notes	Have emailed the author for more information on the allocation process and blinding, and also for more time to first recurrence data: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated (with separate stratification for men and women) to one of four treatment groups"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...acyclovir tablets (Zovirax, Wellcome) 200 mg 5 times daily for seven days; placebo tablets identical to acyclovir taken five times daily for seven days; acyclovir tablets in the above dosage plus co-trimoxazole tablets (Septrin, Wellcome; 160 mg trimethoprim and 800 mg sulphamethoxazole) twice daily for seven days; or placebo tablets identical to acyclovir." "Patients in all four treatment groups were given identical advice regarding additional symptomatic treatment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Two were withdrawn from analysis for failure to comply with study protocol"
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Lai 2000

Methods	Randomised parallel trial Unit of allocation: individuals Number of participants randomised: 28 Number of participants analysed: 28 Number of withdrawals/exclusions: None Source of funding: not reported
Participants	Setting: outpatient, Peking Union Medical College of Dermatology

Lai 2000 *(Continued)*

	Inclusion criteria: first-episode GH; duration no longer than 3 days; no antiviral drug usage in the past week, no syphilis or other disease that can result in genital ulcers **Exclusion criteria**: pregnant or breastfeeding women, abnormal renal or liver functions, immunodeficiency, immunosuppression, or failure of multiple organs, neurological or psychiatric participants; allergic or intolerant to the tested drugs Age: acyclovir group - mean age 33.8 (range 23 to 54); valaciclovir group - mean age 33.5 years (range 22 to 42) Sex: acyclovir group - male - 9, female - 6 valaciclovir group - male - 10, female - 3 Ethnicity: Chinese Type of first-episode herpes: not stated
Interventions	(1) Acyclovir: 1 gm/day, 5 doses of 200 mg daily for 7 to 10 days (2) Valaciclovir: 600 mg day/ two doses of 300 mg daily for 7 to 10 days
Outcomes	Duration of symptoms from onset of treatment Duration of lesions from onset of treatment
Possible conflicts of interest	
Notes	Translated by Ray Zhang

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States “randomization according to stratification”
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding (described as open)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding (described as open)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in analysis
Selective reporting (reporting bias)	Unclear risk	Outcome definitions vague
Other bias	Low risk	No other potential bias identified. Participants comparable at baseline

Levin 1989

Methods	Randomised, parallel trial Unit of allocation: individuals Number of participants randomised: 131 Number of participants analysed: 105 Number of withdrawals/exclusions: 26 (only 3 participants withdrew because of adverse effects - 2 in the high dose rIFN-2A group, the remainder of the participants were excluded because they failed to complete at least 6 months of follow-up) “Twenty-six patients did not complete the study; only three patients withdrew because of adverse effects (two in the high-dose rIFN-2A group). The remainder of the patients were excluded because they failed to complete at least 6 months of follow-up” "65 randomised in rIFN-2A group, 12 did not complete the study with adverse effect data collected from 58 patients. 66 randomised in acyclovir group, 14 did not complete the study but adverse effect data collected from 66 patients" Sources of funding: Hoffmann-La Roche Inc., Nutley, N.J., and the Louis and Sidell Bruckner Memorial Fund
Participants	Setting: participants were enrolled from July 1983 to January 1985 at 4 centres: Denver Disease Control Service, Denver, Colorado; The Fairfax Hospital, Falls Church, Va.; University of California at Los Angeles Herpes Research Clinic, Los Angeles; and the University of Washington Herpes Research Clinic at Harborview Medical Center, Seattle. United States of America **Inclusion criteria**: otherwise healthy individuals, 18 years or older, were eligible for the study if they were entered within 96 hrs of the onset of lesions characteristic of a primary or non-primary initial episode of herpes genitalis. Participants were retained for analysis only if HSV-1 or HSV-2 was isolated from skin or mucus membrane lesions **Exclusion criteria**: participants were excluded if they had underlying medical conditions, were pregnant, used inadequate contraception, had abnormal results in pre therapy laboratory tests, had other dermatologic disease in the genital region, or were unable to complete a 1-year follow-up period Age: (1) Intramuscular injection of rIFN-2A: 25.4 (mean) (2) Topical acyclovir: 26.4 years (mean) Sex: (1) Intramuscular injection of rIFN-2A: male - 17, female - 36 (2) Topical acyclovir: male - 20, female - 32 Type of first-episode herpes: primary and non-primary (not analysed separately)
Interventions	(1) Intramuscular injection of rIFN-2A + topical placebo: rIFN-2A was 18 million IU per injection but then was changed to 9 million IU per injection as the adverse reaction rate for the first 7 participants was unacceptable, given for 9 days on day of entry (day 1), 2, 3, 4 or 5, 7 or 8 and 9. Topical placebo was applied every 4 hours while awake for 7 days (2) Intramuscular placebo + topical acyclovir: Intramuscular placebo was given for 9 days on day of entry (day 1), 2, 3, 4 or 5, 7 or 8 and 9. 5% acyclovir ointment was applied every 4 hours while awake for 7 days All participants received: acetaminophen (650 mg) orally at the time of each injection and every 4 hrs thereafter while participants were awake for 24 hrs
Outcomes	Cessation of pain, fully crusted, skin half-healing, skin fully healed, negative culture, adverse events, mean number of recurrences: per month, first 6 months, second 6 months

Levin 1989 *(Continued)*

Possible conflicts of interest	Author Robert R Scheer is from Hoffmann-La Roche Inc. – the company that funded the trial
Notes	7 participants in the Intramuscular injection of rIFN-2A + topical placebo group received 18 million IU injection and these data are included in the results. Emailed the first author for more details regarding allocation, blinding and outcome assessment and he responded, confirming published information. Due to the age of the study, full details are not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were assigned from a computer-generated list of random numbers to receive…"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded and placebo controlled. Email from first author reported that investigator and subject were both blinded. No further details available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	High risk	20% of participants (26/131) not included in analysis
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Mendelson 1986

Methods	Randomised, double-blind parallel trial Unit of allocation: individuals Number of participants randomised: 31 Number of participants analysed: 31 (17 with initial disease, 14 with primary initial disease) Number of withdrawals/exclusions: 2 women were excluded during the maintenance phase of the study because of non-compliance Sources of funding: the work was supported by a grant from Schering Corporation. Kenilworth, New Jersey, United States of America
Participants	Setting: we studied participants referred to the infectious diseases clinic at this hospital: Division of Infectious Diseases, Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, Canada **Inclusion criteria**: first episodes of GH of less than five days' duration who had no history of vesicular or ulcerative genital lesions. Patients included had no other clinically important disease, were aged 18

Mendelson 1986 *(Continued)*

	or older, and were men or women who were not pregnant and had been taking oral contraceptives or using intrauterine contraceptive devices for at least 3 months before the start of the study **Exclusion criteria**: patients were excluded from the study if they had appreciable secondary genitourinary infections; had any cardiac, hepatic, gastrointestinal, renal, or neurological disease or clotting abnormality; had been exposed to any investigational drug within one month before the start of the study; had been exposed to any other interferon preparations within one month before the start of the study; had received any other systemic antiviral treatment within 30 days before entry to the study; had received any topical antiviral agents within seven days of entry into the study; had any immunosuppressive disease or were receiving immunosuppressive treatment; required concomitant prostaglandin synthetase inhibiting compounds; or yielded negative viral cultures for HSV at the time of enrolment Age: (1) Men: 31 years , women: 27 years (mean) (2) Men: 33 years, women: 25 years Sex: (1) Interferon: male - 6, female - 10 (2) Placebo: male - 7, female - 8 Type of first-episode herpes: primary and non-primary
Interventions	(1) Interferon: subcutaneous interferon 5 X 10^6 IU injections twice daily for 5 days (treatment phase), then subcutaneous interferon 1 X 10^6 IU injections 3 times weekly for 12 weeks (2) Placebo: subcutaneous placebo injections twice daily for 5 days (treatment phase), then subcutaneous placebo injections 3 times weekly for 12 weeks
Outcomes	Mean duration of pain, mean duration of healing, mean duration of itching, mean duration of dysuria, mean duration of inguinal adenopathy, mean duration of vaginal discharge, mean duration of viral shedding, adverse events
Possible conflicts of interest	Unknown
Notes	Cannot find contact email

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“randomised”
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Control patients received placebo injections according to the same schedule"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“Differentiation between the side effects of the interferon and the symptoms of the disease was not possible while the study was blind, but the differences became evident when the code was broken”
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Two women were excluded during the maintenance phase of the study because of non-compliance. The remaining 29 patients completed their entire course of interferon treatment"

Mendelson 1986 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Mertz 1984

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 180 Number of participants analysed: 150 Number of withdrawals/exclusions: 30 (10 were excluded from analysis because of failure to complete the study protocol, 12 were excluded because the antibody specificity of their acute phase serum suggested past HSV-2 infection, and 8 were excluded because HSV was not isolated and a fourfold rise in HSV-2 antibody did not occur) Sources of funding: National Institutes of Health grant AI-20381, Venereal Disease Research Foundation support (for Dr Mertz), and a grant from the Burroughs-Wellcome Co
Participants	Setting: University of Washington, Seattle; University of Vermont, Burlington; University of California-San Diego, La Jolla; University of Alberta, Edmonton; and Sir Mortimer B. Davis-Jewish General Hospital, Montreal. Of the 150 participants who remained for evaluation, 72 were enrolled at the University of Washington, 27 at the University of Vermont, 22 at the University of California-San Diego, 16 at the University of Alberta, and 13 at Jewish General Hospital **Inclusion criteria**: patients with first episodes of GH who were seen within 6 days of the onset of lesions **Exclusion criteria**: pregnant women and women without adequate contraception, menopausal and postmenopausal women, participants younger than 18 and older than 50 years, participants who had used any form of antiviral or immunostimulant therapy, participants who were immunosuppressed, and participants with significant renal or hepatic disease Age: (1) Primary - Oral acyclovir: 26 years (mean) (2) Primary - Placebo: 25.6 years (mean) (3) Non-primary - Oral acyclovir: 27.3 years (mean) (4) Non-primary - Placebo: 27.7 years (mean) Sex: (1) Primary - Oral acyclovir: male - 23, female - 38 (2) Primary - Placebo: male - 21, female - 37 (3) Non-primary - Oral acyclovir: male - 3, female - 9 (4) Non-primary - Placebo: male - 8, female - 11 Type of first-episode herpes: primary and non-primary
Interventions	(1) Oral acyclovir: 200 mg acyclovir in capsule taken orally 5 x daily for 10 days (2) Placebo: placebo capsule taken orally 5 x daily for 10 days

Mertz 1984 *(Continued)*

Outcomes	Duration of pain, duration of dysuria, duration of any constitutional symptoms, time to crusting, time to healing, % forming new lesions after 48 hr of therapy, viral shedding: all genital lesions, cervix, time to first recurrence, adverse events
Possible conflicts of interest	Author Dr. Keeney is from Burroughs-Wellcome which helped fund this study
Notes	Have email regarding randomisation, allocation, blinding, and outcome assessment: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“patients were randomly assigned”
Allocation concealment (selection bias)	Unclear risk	"double-blind, placebo-controlled trial"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"patients were randomly assigned capsules containing 200 mg of acyclovir or placebo in a coded container"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data missing for 17% (30/180) of participants
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Mindel 1982

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 30 Number of participants analysed: 30 Number of withdrawals/exclusions: not mentioned Sources of funding: unknown
Participants	Setting: the Department of Genito-urinary medicine, Middlesex Hospital, London, United Kingdom. **Inclusion criteria**: within 6 days of the first appearance of genital sore **Exclusion criteria**: history of previous GH, age less than 16 years, renal impairment, or specific antiviral therapy in the previous 14 days. Females were excluded if they were pregnant or were not using adequate contraceptive measures (oral contraception or intrauterine device)

Mindel 1982 *(Continued)*

	Age: (1) Acyclovir: 22 (median), 18 to 43 (range) (2) Placebo: 21 (median), 16 to 31 (range) Sex: (1) Acyclovir: female - 12, male - 3 (2) Placebo: female - 12, male - 3 Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: acyclovir 5 mg/kg 45 to 60 min intravenous infusions through an indwelling intravenous cannula every 8 hours (except for the first 4 participants who had a bolus injection) for 15 doses (2) Placebo: mannitol 45 to 60 min intravenous infusions through an indwelling intravenous cannula every 8 hours (except for the first 4 participants who had a bolus injection) for 15 doses
Outcomes	Viral shedding time (all lesions), duration of new lesion formation, duration of vesicles, duration pain, duration all symptoms, healing time (all lesions), time to first recurrence, adverse events
Possible conflicts of interest	A Paul Fiddian is an author of "Wellcome Research Laboratories", "We thank Mrs C A Burke, Clinical Research Division, Wellcome Research Laboratories, for statistical analysis"
Notes	Data in median form. Included if presented within 6 days. Emailed asking for raw data, and details on randomisation, blinding, allocation and outcome assessment and received a response: due to the age of the studies, the raw data and details are no longer available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“We conducted a randomised, double-blind, placebo-controlled trial”
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“We conducted a randomised, double-blind, placebo-controlled trial.” “The drug and placebo were packaged in indistinguishable vials with individual code numbers, so that the trial was double-blind”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be complete
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Mindel 1986

Methods	Randomised, placebo-controlled, parallel trial

Mindel 1986 *(Continued)*

	Unit of allocation: individuals Number of participants randomised: 60 Number of participants analysed: 60 Number of withdrawals/exclusions: 1 (all but one of the participants were followed up for at least six months; the exception was a patient receiving a short course of treatment, who was lost to follow-up after 37 days) Sources of funding: not stated
Participants	Setting: Women participants attending the genitourinary clinic of Middlesex Hospital Medical School, London, England, United Kingdom **Inclusion criteria**: women participants attending the genitourinary clinic of this hospital within five days of a first attack of GH were offered the opportunity of participating in the study. We limited the study to women participants as they usually have more severe infections **Exclusion criteria**: a history of previous GH, age less than 16 years, renal impairment, or specific antiviral therapy in the previous 14 days. Females were excluded if they were pregnant or were not using adequate contraceptive measures (oral contraception or intrauterine device) Age: (1) Prolonged course of acyclovir: 24.3 (mean), 5.7 SD (2) Short course of acyclovir: 25.2 (mean), 7 SD Sex: All women Type of first-episode herpes: unknown
Interventions	(1) Prolonged course of acyclovir: 200 mg acyclovir taken orally 5 x daily for 5 days, then 4 x daily for 37 days (2) Short course of acyclovir: 200 mg acyclovir taken orally 5 x daily for 5 days, then placebo 4 x daily for 37 days
Outcomes	Local symptoms, systemic symptoms, viral shedding, healing, frequency of recurrence a month, adverse events
Possible conflicts of interest	IV Weller is a Wellcome Trust Senior Lecturer in Infectious Diseases
Notes	Data is in median form. Emailed asking for raw data, and details on randomisation, blinding, allocation, and outcome assessment and received a response: due to the age of the studies, the raw data and details are no longer available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“We randomised patients into two treatment groups”
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was a placebo group, but no further details given

Mindel 1986 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was a placebo group, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient lost to follow-up after 37 days"
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Mindel 1987

Methods	Randomised, double-blind, parallel trial Unit of allocation: individuals Number of participants randomised: 88 Number of participants analysed: 77 Number of withdrawals/exclusions: 11 (8 who were lost to follow-up after the initial visit, 1 who lost her tablets, 1 who proved to have varicella zoster and not HSV, and 1 who was virus-negative with no antibody response) Sources of funding: not stated
Participants	Setting: Departments of Genitourinary Medicine at the Middlesex Hospital, London, or the Royal Hallamshire Hospital, Sheffield. United Kingdom **Inclusion criteria**: first attack of GH presenting within 5 days of onset **Exclusion criteria**: patients under 16 years; females not using adequate contraception; participants unable to attend at the required intervals, and those who had used any antiviral drugs in the preceding 2 weeks; participants with a history of gout, hyperuricaemia, or immunodepression. Since a high proportion of men attending the Middlesex Hospital clinic were homosexual, with a high attendant prevalence of HIV infection, all men from this centre were excluded Age: (1) Acyclovir: 25.5 (mean), 7.02 SD (2) Inosine pranobex: 23.3 (mean), 4.9 SD (3) Both: 24.3 (mean), 7.9 SD Sex: (1) Acyclovir: women - 21, men - 3 (2) Inosine pranobex: women - 24, men - 4 (3) Both: women - 21, men - 4 Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: 200 mg acyclovir taken orally 4 x daily for 7 days, "dummy" inosine pranobex taken orally 4 x daily for 7 days (2) Inosine pranobex: 1 g inosine pranobex taken orally 4 x daily for 7 days, "dummy" acyclovir taken orally 4 x daily for 7 days

Mindel 1987 *(Continued)*

	(3) Both: 200 mg acyclovir taken orally 4 x daily for 7 days, 1 g inosine pranobex taken orally 4 x daily for 7 days
Outcomes	All participants: viral shedding, dysuria, all symptoms, healing; women: viral shedding, dysuria, all symptoms, healing; adverse events
Possible conflicts of interest	"We thank the Wellcome Research Laboratories in Beckenham, Kent, for help and support"
Notes	Data is in median form. Emailed asking for raw data, and details on randomisation, blinding, allocation, and outcome assessment and received a response: due to the age of the studies, the raw data and details are no longer available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Patients were randomly allocated”
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12.5 % of data missing (11/88)
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Niimura 1996

Methods	Randomised parallel trial Unit of allocation: individuals Number of participants randomised: 161 (made up of first-episode GH and kaposi's varicelliform eruption) Number of participants analysed: 85 (first-episode GH) Number of withdrawals/exclusions: 34 (14 - mild disease, 1 - too severe, 5 - lost after first visit, 4 - patient withdrawal, 1 - diagnosis changed, 9 - unclear) Sources of funding: Not reported.
Participants	Setting: both outpatient and inpatient setting in 60 Hospitals all over Japan.

Niimura 1996 *(Continued)*

	Inclusion criteria: patients (male and female), 16 years and older, with their first episode of GH HSV infection. Included as soon as possible **Exclusion criteria**: Patients with renal dysfunction, patients with severe liver dysfunction, or severe cardiovascular dysfunction, patients with severe underlying medical problem (especially patients with severely weakened immune system), patients who were administered other antiviral drugs (acyclovir, vidarabine, or interferon etc), or gamma globulin preparations within two weeks prior to the trial, patients with gestation, possibility of gestation or breast feeding, patients whom a primary physician assesses unsuitable Patient characteristics: patients with first-episode GH were not subgrouped Type of first-episode herpes: unclear
Interventions	(1) Famciclovir 125 mg tablets orally 3 x daily for 5 days (2) Famciclovir 250 mg tablets orally 3 x daily for 5 days (3) Famciclovir 500 mg tablets orally 3 x daily for 5 days
Outcomes	Overall improvement, residual lesion ratio
Possible conflicts of interest	Analyses of study were completed by SmithKline Beecham
Notes	Japanese study translated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	A rule for allocating interventions to participants is not specified. No explanation of the choice of 60 hospitals
Allocation concealment (selection bias)	High risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All incomplete outcome data was addressed in detail
Selective reporting (reporting bias)	Low risk	All outcomes seemed to be reported
Other bias	High risk	Famciclovir in this study was made in SmithKline Beecham. Data analyses in this study were done by SmithKline Beecham

Nilsen 1982

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 116 (31 initial, 85 recurrent) Number of participants analysed: 31 (initial) Number of withdrawals/exclusions: not mentioned Sources of funding: Grant from Wellcome Foundation Ltd (Detailed in preliminary study)
Participants	Setting: Special clinics of the University Hospital, Bergen, the Municipal Health Centre, Oslo, and the Karnsjukhuset, Skovde **Inclusion criteria**: presented within 5 days of onset of lesions if initial, and within 48 hours if recurrent **Exclusion criteria**: under 16 years, pregnant women, not adequately protected against pregnancy, concomitant other infections, treatment with other antivirals, participants not giving informed consent Age: (1) Acyclovir: 26.5 years (mean) (2) Placebo: 24.8 years (mean) (participants with first-episode GH) Sex: (1) Acyclovir: male - 7, female - 10 (2) Placebo: male - 7, female - 7 Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: 2 100 mg oral capsules, for 5 days, 5 x a day (2) Placebo: 2 placebo oral capsules, for 5 days, 5 x a day
Outcomes	Duration of pain, duration of all symptoms, duration of viral shedding, duration of itching, new lesion formation, assessed healing time, averaged healing time, crusting time, cessation of new lesions, adverse events
Possible conflicts of interest	Dr. Fiddian is from Wellcome Research Lab
Notes	Data is in median form. Emailed to try and obtain data in raw form: no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Random allocation according to a predetermined code”
Allocation concealment (selection bias)	Unclear risk	“Patients were randomly allocated under double-blind conditions”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	“The trial was double-blind and placebo-controlled”. Emailed regarding details of blinding: no response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given

Nilsen 1982 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"2 patients in the acyclovir group and 1 patient in the placebo group were lost to follow-up before completion of therapy and have been excluded from the safety analysis"
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Pazin 1987

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 69 Number of participants analysed: 64 Number of withdrawals/exclusions: 5 (due to lack of virological confirmation of diagnosis) Sources of funding: this work was supported by contract AI-02661 from the National Institute of Allergy and Infectious Diseases and grant RR-00056 from the Division of Research Resources, National Institutes of Health
Participants	Setting: 62 of the qualified participants were enrolled in Pittsburg and the remaining two in Rochester, New York **Inclusion criteria**: eligible participants had lesions for less than 72 hrs; no prior history of GH; a negative pregnancy test (urine chorionic gonadotropin test and confirmatory serum assay); no major cardiac, renal, or pulmonary disease; no personal, emotional, or professional factors that could be expected to interfere with the course of treatment or follow-up; no psychiatric or addictive disorders that could preclude informed consent; a leukocyte count of ≥5,000/mm^3, a platelet count of ≥ 100,000/mm^3, and a haemoglobin level of ≥ 12g /dl **Exclusion criteria**: lack of virological confirmation of diagnosis Age: (1) Interferon: 25.8 years (mean), 18 to 40 years (range) (2) Placebo: 24.9 years, 17-38 years Sex: all women Type of first-episode herpes: primary and non-primary
Interventions	(1) Interferon: on the day of enrolment, the patient received 2 doses of interferon (5 x 10^4 U/kg) by intramuscular injection. On the 2nd day, 3rd, 4th, 5th, 6th, 7th, 8th, and 10th, 12th, and 14th, single doses were given. The total amount of interferon received over 14 days was 6 x 10^5 U/kg (2) Placebo: on the day of enrolment, the patient received 2 doses of an equivalent volume of 4.5 mg of human serum albumin/ml by intramuscular injection. On the 2nd day, 3rd, 4th, 5th, 6th, 7th, 8th, and 10th, 12th, and 14th, single doses were given
Outcomes	Pain, time to healing, time to first recurrence, duration of viral shedding, frequency of recurrences, adverse effects
Possible conflicts of interest	Unknown

Pazin 1987 *(Continued)*

Notes	More details provided on interferon preparation. Full results not provided, and more information required on allocation and blinding - have emailed: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to receive interferon or placebo"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the clinical personnel nor the patient knew which group she was in"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the clinical personnel nor the patient knew which group she was in" - probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	64/69 (93%) participants analysed
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Peacock 1988

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 105 Number of participants analysed: 82 Number of withdrawals/exclusions: 23 (7 because of misdiagnoses or protocol violations and 16 because of failure to obtain a positive pre-therapy culture result for HSV) Sources of funding: this work was supported in part by a grant from the Burroughs Wellcome Company and in part by Training Grant AI-07001 from the National Institute of Allergy and Infectious Diseases (University of North Carolina-Chapel Hill) and General Clinical Research Center Grant RR-032 (University of Alabama-Birmingham)
Participants	Setting: participating centres included the University of North Carolina at Chapel Hill, the University of Alabama at Birmingham, New York University, the University of California, Los Angeles, and Duke University. United States of America **Inclusion criteria**: males and females older than 15 years of age with no prior history of genital HSV infection, a clinical diagnosis of GH with extensive genital lesions present for less than 7 days, and systemic symptoms or signs such as fever, tender lymphadenopathy, headaches, and so forth. All participants were otherwise in good general health

Peacock 1988 *(Continued)*

	Exclusion criteria: pregnancy or ineffective contraceptive methods in females, significant pre-existing hepatic or renal dysfunction, and antiviral or immunomodulating therapies given within the previous 10 days or 30 days, respectively Age: (1) Acyclovir: 24.5 years (mean) (2) Placebo: 23.5 years (mean) Sex: (1) Acyclovir: male - 11, female - 31 (2) Placebo: male - 13, female - 27 Type of first-episode herpes: primary and non-primary
Interventions	(1) Acyclovir: acyclovir 5 mg/kg of body weight given intravenously every 8 hours over 60 minutes for 5 days (i.e. 15 doses) (2) Placebo: normal saline given intravenously every 8 hours over 60 minutes for 5 days (i.e. 15 doses)
Outcomes	Viral shedding: all lesions, group 1 lesions; median duration of pain after onset of therapy; crusting - all lesions; healing - all lesions, group 1 lesions; incidence of recurrence; time to first recurrence; adverse effects of therapy
Possible conflicts of interest	Gail M Knowlton and L Gray Davis are from the company which funded the research
Notes	Data is in median form. Wanted to contact for details of randomisation and blinding, for the total participants followed up and also for the raw data so we can use the data in the meta-analysis however could not find contact details. There are more participants in the adverse event groups than are analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Patients were then randomly assigned”
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	22% participants (23/105) not included in analysis
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Silvestri 1982

Methods	Randomised, double-blind, placebo-controlled, parallel trial Unit of allocation: individuals Number of participants randomised: 58 Number of participants analysed: 32 (primary GH) Number of withdrawals/exclusions: 26 (21 had HSV antibody present in the first serum obtained, providing serological evidence of previous HSV infection. Of the remaining 37 participants with primary infection, five were excluded from analysis because of negative culture results or inadequate follow-up) Sources of funding: National Institutes of Health Grant AI-14495 and program project grant AI-12191, Public Health Service project grant SEA-78-06-72, and grants from Research Industries, Salt Lake City, and the Bureau of Medical Services
Participants	Setting: patients with genital HSV infection who were referred to the University of Washington Herpes Clinics at either the Harborview Medical Center or the University of Washington Student Health Center, Seattle, were enrolled in the study **Inclusion criteria**: all were at least 18 years of age and otherwise in good health. Patients were enrolled only if initial lesions had been present no more than 8 days Type of first-episode herpes: primary and non-primary
Interventions	(1) Idoxuridine: 8 ml treatment vial of topical 30% weight per volume idoxuridine in 100% dimethyl sulfoxide applied topically 4 x daily with a cotton tipped applicator for 7 days (2) Dimethyl sulfoxide alone: 8 ml treatment vial of 100% dimethyl sulfoxide applied topically 4 x daily with a cotton tipped applicator for 7 days (3) Normal saline: 8 ml treatment vial of normal saline applied topically 4 x daily with a cotton tipped applicator for 7 days
Outcomes	Symptoms, mean no. of days after initiation of treatment: tender lymphadenopathy, pain, dysuria, vaginal discharge; viral shedding: mean no. of days from initiation of treatment to last positive HSV culture result, participants shedding virus during treatment, %, mean duration of viral shedding, days; mean no. of days from initiation of treatment to healing; mean no. of days from initiation of treatment to crusting; mean no. of days from onset of lesions to healing, participants in whom new lesions developed during treatment, %; time to first recurrence; adverse events
Possible conflicts of interest	Unknown
Notes	Have emailed for more information required on demographics and allocation: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“patients were assigned randomly”
Allocation concealment (selection bias)	Low risk	“All treatment solutions were prepared and dispensed into identical, coded vials by a pharmacist and technician who were not otherwise involved in the study”

Silvestri 1982 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All treatment solutions were prepared and dispensed into identical, coded vials by a pharmacist and technician who were not otherwise involved in the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but no further details given about outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 55% (32/58) participants analysed. Unclear why (or whether) 21 participants with non-primary infection were randomised then excluded, as they appear to meet study inclusion criteria
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Low risk	No other potential bias identified

Wald 1994

Methods	Randomised, parallel, double-blind, comparative trial Unit of allocation: individuals Number of participants randomised: 139 Number of participants analysed: 87 Number of withdrawals/exclusions: 52 (4 did not have culture proven herpes, 9 did not start taking the drug within 5 days, 29 had evidence of recurrence rather than first-episode disease, 10 failed to return to a follow up appointment) Sources of funding: Burroughs Wellcome and National Institutes of Health
Participants	Setting: University of Washington Viral Disease Research Clinic at Harbour View Medical Centre, Seattle, Washington, United States of America **Inclusion criteria**: healthy women and men with first episode of GH, no prior antiviral therapy **Exclusion criteria**: did not have culture proven herpes, did not start taking the drug within 5 days, evidence of recurrent disease, pregnancy Age: (1) 22 (median), 17 to 39 (range) (2) 22 (median), 18 to 33 (range) Sex: (1) male: 21 (36%), female: 38 (64%) (2) male: 4 (14%), female: 24 (86%) Type of first-episode herpes: primary and non-primary
Interventions	(1) High dose acyclovir: oral 800 mg for 10 days, 5 x a day (2) Low dose acyclovir: oral 200 mg for 10 days, 5 x a day
Outcomes	Duration of symptoms from onset of treatment, duration of lesions from onset of treatment, time to first recurrence

Wald 1994 *(Continued)*

Possible conflicts of interest	Gray Davis is from the company producing the drug
Notes	Emailed to try and obtain raw data so results can be used in the meta-analysis: it is not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomised to one of the following regimes". Emailed author and they responded saying they no longer have record of the process
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Subjects and investigators were blinded to the group assignment". Emailed author and they responded saying they no longer have record of the process
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participants and investigators were blinded to the group assignment: no further details about outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 82/139 (59%) of participants analysed
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Significant differences between groups at baseline in gender balance and symptom severity

Zavala 1988

Methods	Randomised, parallel, double-blind, parallel trial Unit of allocation: individuals Number of participants randomised: 60 Number of participants analysed: 60 Number of withdrawals/exclusions: 0 Sources of funding: No information provided
Participants	Setting: outpatient clinic of Hospital Angel Leaño. Guadalajara, Jalisco **Inclusion criteria**: patients from both sexes aged 18 to 48 years, diagnosis of primary GH, confirmatory ELISA test **Exclusion criteria**: duration of disease more than 3 days, co-morbidities (any additional disease), treatment with antivirals prior to the beginning of the study Demographic information: "No se encontraron diferencias significativas en cuanto a sexo, edad, peso, días de evolución del padecimiento, temperatura, presencia de vesículas, intensidad del dolor y

Zavala 1988 *(Continued)*

	malestar general antes del tratamiento." "*We found no significant differences with respect to sex, age, weight, days of evolution, temperature, presence of vesicles, pain intensity and general discomfort before treatment"* Type of first-episode herpes: not specified
Interventions	(1) Ribavirin: 400 mg ribavirin every 8 hours taken orally for 10 days (2) Placebo: placebo every 8 hours taken orally for 10 days
Outcomes	Average duration of pain, number of vesicles (average), number of recurrences in 30 days after onset of treatment, adverse events
Possible conflicts of interest	No information available
Notes	Data was extracted by Luis Carlos Salazar Díaz. Article in Spanish. Only one person extracted data. Have not made contact for more information at this stage on the basis of language

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Se realizó un estudio prospectivo, doble ciego al azar, en 60 pacientes (…)” *"We performed a prospective, randomised double-blind study, in 60 patients (...)"* The randomisation method is not stated
Allocation concealment (selection bias)	Unclear risk	The allocation concealment method is not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	“…el tratamiento consistió en la administración oral de ribavirina (400 mg/8 horas) o placebo, durante 10 días, ambos presentados en idéntica forma farmacéutica” *“... the treatment consisted of oral administration of ribavirin (400 mg/8 hours) or placebo for 10 days, both delivered in the same pharmaceutical form"* It does not state how personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“Se realizó un estudio prospectivo, doble ciego al azar, en 60 pacientes (…)” *"We performed a prospective, randomised double-blind study, in 60 patients (...)"* It was a double-blind placebo controlled trial. The blinding procedure was not explained
Incomplete outcome data (attrition bias) All outcomes	Low risk	None were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The report showed all the outcomes specified in the methods section of the report, as well as, all the expected outcomes for the year of the study (1988) There is not data concerning pregnant women. Protocol not available
Other bias	Low risk	No other potential bias identified

ELISA: enzyme-linked immunosorbent assay

GH: genital herpes
HSV: herpes simplex virus
HSV-1: herpes simplex virus type 1
HSV-2: herpes simplex virus type 2
ITT: intention-to-treat
IU: international units
IV: intravenous
rIFN-2A: intramuscular recombinant alpha interferon
SD: standard deviation
SEM: standard error of the mean
STD: sexually transmitted diseases

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Hasani 1986	Did not separate out first episode and recurrent genital herpes
Anonymous 1985	Review
Anonymous 1997	Only reference is news article cited. Attempts to obtain more details from manufacturers (Glaxo) were unsuccessful
Anonymous 2004	Not randomised
Armstrong 1983	Not a RCT and not looking at first episode genital herpes
Ashley 1984	Not randomised
Ashley 1988	Not randomised
Baeten 2008	Not first episode genital herpes
Balfour 1994	An HIV trial not HSV
Beeson 2002	Facial infection
Belec 2006	Not first-episode genital herpes
Bernstein 1984	Not randomised
Bierman 1981	Recurrent genital herpes
Blough 1979	No mention of randomisation
Bollen 2008	Not first episode genital herpes
Brocklehurst 1990	Letter not RCT
Cattamanchi 2011	HIV trial rather than first-episode genital herpes
Celum 2008	Not first-episode genital herpes
Celum 2010	Not first-episode genital herpes
Chen 2000	Unclear what proportion of participants had first-episode infection. Repeated attempts to contact study authors unsuccessful

Study	Reason for exclusion
Clewell 2012	Results not separated into initial and recurrent infection. Also studied other forms of herpes that was not analysed separately. Emailed for more information: Dynamiclear responded and said there was no division between first-episode and recurrent genital herpes, or between genital and facial herpes
Conant 2002	Recurrent genital herpes
Cowan 2008	Not separated into initial and recurrent infection
Crespi 1988	Not separated into initial and recurrent infection
Dannenmaier 1985	Not solely genital or first-episode
Delany 2009	Not separated into initial and recurrent infection
Diaz-Mitoma 1998	Recurrent genital herpes
Drake 2010	Not first-episode genital herpes
Drake 2012	Not first-episode genital herpes
Emoedi 1983	Not first-episode genital herpes
Fife 2008	Randomisation takes place following lesion healing
Garcia 2001	Not randomised
Glezerman 1988	Not first-episode genital herpes
Goodman 1975	Viral shedding was primary outcome, which is not relevant to our review
Guillaume 2002	Not randomised
Gunby 1983	Not randomised
Guo 2001	Does not mention "first-episode" herpes
Guo 2002	Does not mention "first-episode" herpes
Handsfield 2007	Randomisation takes place following lesion healing
Harris 1995	Review
Haverkos 1980	Recurrent herpes labialis
Hellgren 1983	Not first-episode genital herpes
Hilton 1978	Mostly recurrent genital herpes. Does not appear to be randomised. Emailed authors: no information able to be provided
Hjorth 1982	Study of recurrent herpes labialis
Holzgreve 2005	Not randomised. Not first-episode genital herpes
Hu 2001	Participants with first-episode disease not reported separately from those with recurrence

Study	Reason for exclusion
Hudson 2004	Review
Johnston 2011	Emailed authors and more information was provided: was not first-episode genital herpes
Johnston 2012	Emailed authors and more information was provided: was not first-episode genital herpes
Jones 1979	Not first-episode genital herpes
Kalinin 1990	Review
Kaufman 1978	Uses an antiseptic intervention
Koytchev 1999	Not first-episode genital herpes
Kuang 2008	Does not mention "first-episode" herpes
LeGoff 2007	Not first-episode genital herpes
Leone 2007	Does not report on outcomes of interest
Levien 1995	Review
Li 1998	Insufficient information as to which participants had first-episode genital herpes: 16 of 22 patients (73%) in the treatment group were “first-episode“; unclear in the control group
Loveless 1997	Re-publication of three already included studies: Bryson 1983; Mertz 1984; Nilsen 1982
Macotela 1984	Looking at recurrent genital herpes
Mark 2007	Study of recurrent genital herpes
Martens 2009	Emailed to try to find out whether treatment was given while the patients were still experiencing their first-episode genital herpes: no response
Mayaud 2009	Emailed authors and more information was provided: was not first-episode genital herpes
Meyers 1982	Emailed Dr. Balfour asking whether the participants had first-episode or recurrent genital herpes. He replied "None of the Minnesota subjects had genital herpes. I have no data from other centres"
Nagot 2007	Not first-episode genital herpes
Niimura 1987	First-episode genital herpes was not separated from recurrent episodes
Nunes 2008	Not first-episode genital herpes
Pang 2003	Does not mention "first-episode" herpes
Paz-Bailey 2009	Not first-episode genital herpes. Emailed for more information: no response
Petersen 1993	Results for first-episode and recurrent episodes are not provided separately
Phiri 2010	Results of first-episode genital herpes not reported
Posevaia 1991	Not looking at treatment

Study	Reason for exclusion
Qadripur 1976	Does not mention first-episode. Only 3 of 41 have genital herpes
Rompalo 1988	First-episode rectal herpes
Roy 1982	Not an antiviral
Ruhnek-Forsbeck 1985	Review
Safrin 1991	Not first-episode genital herpes
Safrom 1995	Not first-episode genital herpes
Saltzman 1994	Review
Schacker 1998	Not first-episode genital herpes
Schneider 1985	Herpes labialis only
Scott 1996	There were no data for first-episode
Scott 2001	Not randomised. No comparison group
Skinner 1983	Recurrent herpes
Sperling 2008	Treatment is suppression
Strachan 2011	Not first-episode genital herpes
Strand 2004	Recurrent genital herpes
Syed 1995a	Fraud
Syed 1995b	Fraud
Syed 1995c	Fraud
Syed 1997a	Fraud
Syed 1997b	Fraud
Syed 1998a	Fraud
Syed 1998b	Fraud
Tardivo 2012	Did not mention first-episode genital herpes
Taylor 1975	Not randomised
Twiss 2011	Not first-episode genital herpes
Vazquez 1998	Not randomised
Vennemann 1985	Not first-episode genital herpes. Does not appear to be randomised
Wald 1995	Not randomised

Study	Reason for exclusion
Wald 1996	Not first-episode genital herpes
Wald 2008	Unclear whether first-episode and not analysed separately
Walker 1985	Review
Wenner 2005	Not randomised
Wenz 1981	Advertisement for study participation
Whitley 1984	Not first-episode genital herpes
Yarnell 2009	Not randomised
Zu 2010	Laboratory-based study

HSV: herpes simplex virus
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Grebeniuk 1981

Methods	
Participants	
Interventions	
Outcomes	
Notes	Waiting for full-text translation for assessment for inclusion. In Russian

Skerk 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	Set for inclusion. Waiting for full-text translation. In Croatian

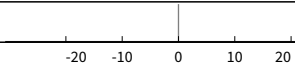
DATA AND ANALYSES

Comparison 1. Oral acyclovir versus placebo

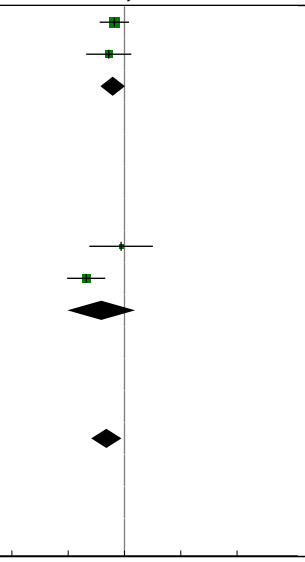
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of symptoms from onset of treatment	2	82	Mean Difference (IV, Random, 95% CI)	-3.22 [-5.91, -0.54]
1.1 Men	2	33	Mean Difference (IV, Random, 95% CI)	-2.10 [-4.28, 0.09]
1.2 Women	2	49	Mean Difference (IV, Random, 95% CI)	-4.13 [-10.15, 1.89]
2 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Any adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Dizziness	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Coryza	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Urticaria	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Tiredness	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Gastrointestinal discomfort	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Renal colic	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Sciatica	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.11 Increased serum creatinine	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.12 Decreased red blood cell count	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Duration of lesions from onset of treatment	2	86	Mean Difference (IV, Fixed, 95% CI)	-3.51 [-6.19, -0.82]
3.1 Men	2	35	Mean Difference (IV, Fixed, 95% CI)	-5.74 [-9.80, -1.69]
3.2 Women	2	51	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-5.34, 1.85]

Analysis 1.1. Comparison 1 Oral acyclovir versus placebo, Outcome 1 Duration of symptoms from onset of treatment.

Study or subgroup	Acyclovir N	Acyclovir Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 Men							

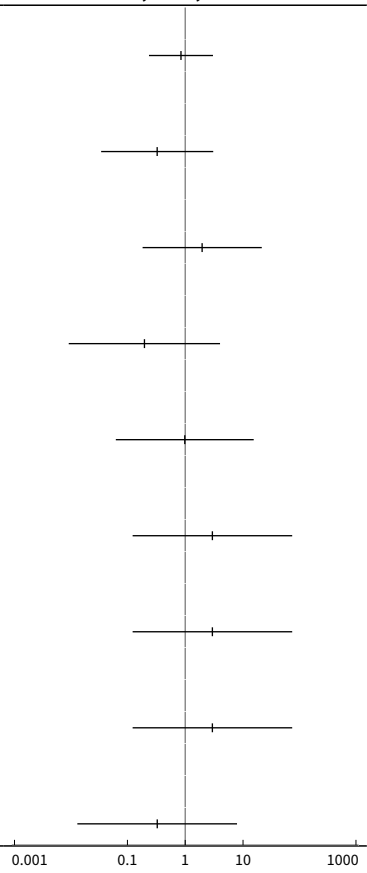


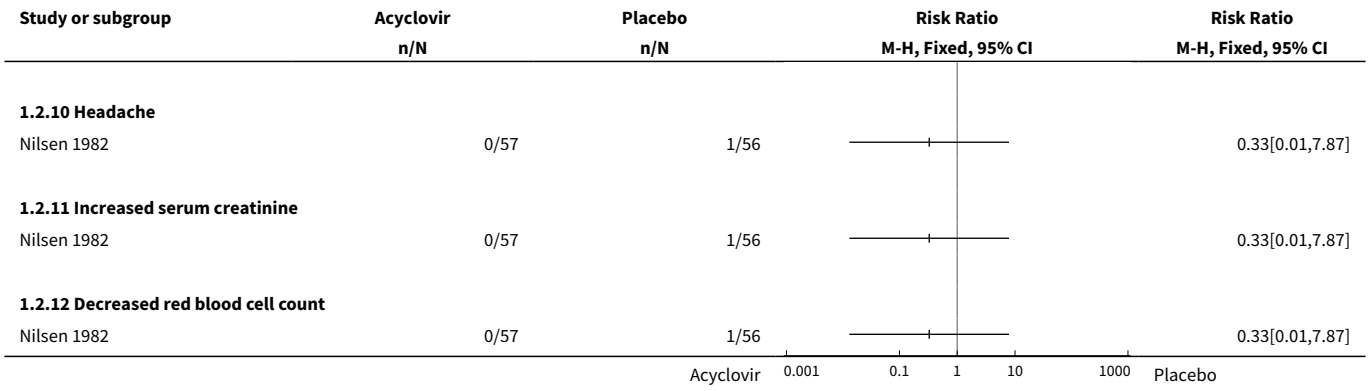
Study or subgroup	Acyclovir N	Acyclovir Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bryson 1983	7	2 (1.6)	8	3.8 (3.4)		33.55%	-1.8[-4.4,0.8]
Kinghorn 1986b	9	7.6 (2)	9	10.4 (5.8)		23.42%	-2.8[-6.81,1.21]
Subtotal ***	**16**		**17**			**56.97%**	**-2.1[-4.28,0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%							
Test for overall effect: Z=1.88(P=0.06)							
1.1.2 Women							
Bryson 1983	15	2.8 (7.1)	14	3.4 (8.3)		15.5%	-0.6[-6.24,5.04]
Kinghorn 1986b	10	8.4 (2.2)	10	15.2 (5)		27.53%	-6.8[-10.19,-3.41]
Subtotal ***	**25**		**24**			**43.03%**	**-4.13[-10.15,1.89]**
Heterogeneity: Tau^2=13.59; Chi^2=3.41, df=1(P=0.06); I^2=70.69%							
Test for overall effect: Z=1.34(P=0.18)							
Total ***	**41**		**41**			**100%**	**-3.22[-5.91,-0.54]**
Heterogeneity: Tau^2=3.84; Chi^2=6.31, df=3(P=0.1); I^2=52.47%							
Test for overall effect: Z=2.35(P=0.02)							
Test for subgroup differences: Chi^2=0.39, df=1 (P=0.53), I^2=0%							



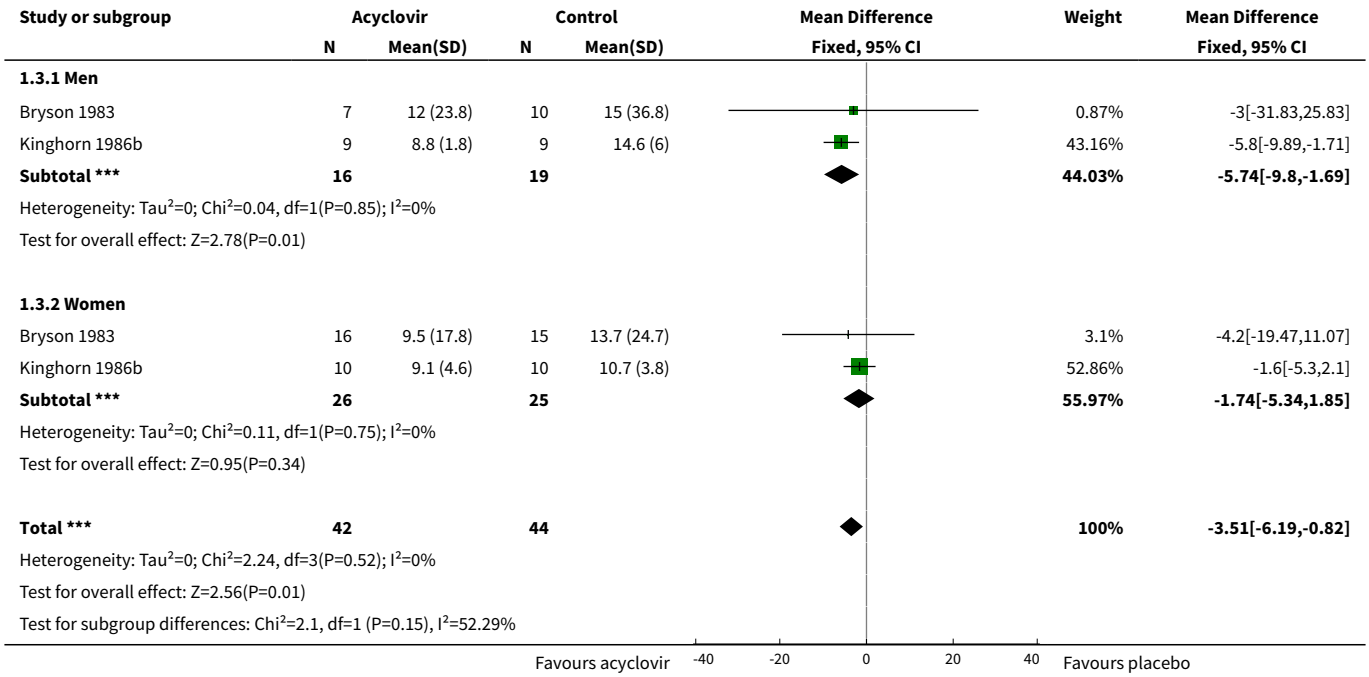
Analysis 1.2. Comparison 1 Oral acyclovir versus placebo, Outcome 2 Adverse events.

Study or subgroup	Acyclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Any adverse event				
Mertz 1984	4/73	5/77		0.84[0.24,3.02]
1.2.2 Dizziness				
Nilsen 1982	1/57	3/56		0.33[0.04,3.05]
1.2.3 Coryza				
Nilsen 1982	2/57	1/56		1.96[0.18,21.06]
1.2.4 Urticaria				
Nilsen 1982	0/57	2/56		0.2[0.01,4]
1.2.5 Tiredness				
Nilsen 1982	1/57	1/56		0.98[0.06,15.32]
1.2.6 Diarrhoea				
Nilsen 1982	1/57	0/56		2.95[0.12,70.87]
1.2.7 Gastrointestinal discomfort				
Nilsen 1982	1/57	0/56		2.95[0.12,70.87]
1.2.8 Renal colic				
Nilsen 1982	1/57	0/56		2.95[0.12,70.87]
1.2.9 Sciatica				
Nilsen 1982	0/57	1/56		0.33[0.01,7.87]





Analysis 1.3. Comparison 1 Oral acyclovir versus placebo, Outcome 3 Duration of lesions from onset of treatment.



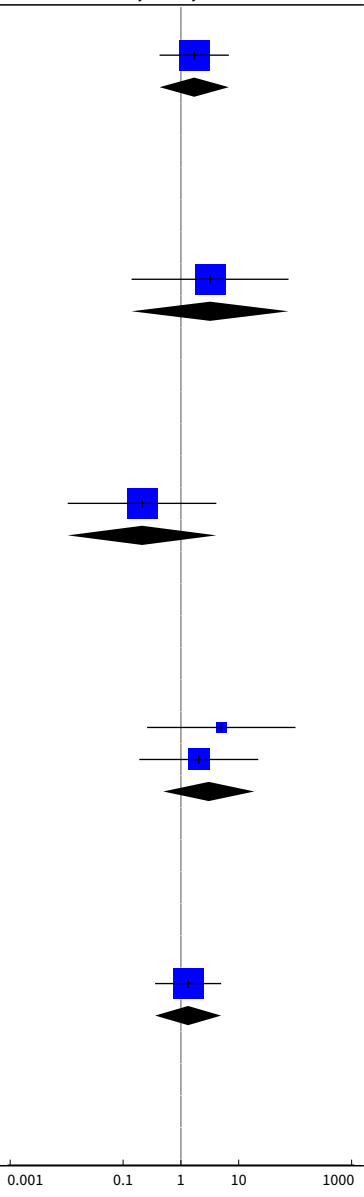
Comparison 2. Intravenous acyclovir versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All adverse effects	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.43, 6.75]
1.2 Phlebitis	1	31	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [0.14, 72.69]
1.3 Maculopapular eruption	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Nausea	2	135	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.49, 18.59]
1.5 Abnormal liver function tests	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.36, 4.97]

Analysis 2.1. Comparison 2 Intravenous acyclovir versus placebo, Outcome 1 Adverse events.

Study or subgroup	Acyclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 All adverse effects					
Peacock 1988	5/52	3/53		100%	1.7[0.43,6.75]
Subtotal (95% CI)	**52**	**53**		**100%**	**1.7[0.43,6.75]**
Total events: 5 (Acyclovir), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
2.1.2 Phlebitis					
Corey 1983	1/15	0/16		100%	3.19[0.14,72.69]
Subtotal (95% CI)	**15**	**16**		**100%**	**3.19[0.14,72.69]**
Total events: 1 (Acyclovir), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					
2.1.3 Maculopapular eruption					
Corey 1983	0/15	2/16		100%	0.21[0.01,4.1]
Subtotal (95% CI)	**15**	**16**		**100%**	**0.21[0.01,4.1]**
Total events: 0 (Acyclovir), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.03(P=0.3)					
2.1.4 Nausea					
Mindel 1982	2/15	0/15		33.55%	5[0.26,96.13]
Peacock 1988	2/52	1/53		66.45%	2.04[0.19,21.8]
Subtotal (95% CI)	**67**	**68**		**100%**	**3.03[0.49,18.59]**
Total events: 4 (Acyclovir), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.22, df=1(P=0.64); I^2=0%					
Test for overall effect: Z=1.2(P=0.23)					
2.1.5 Abnormal liver function tests					
Mindel 1982	4/15	3/15		100%	1.33[0.36,4.97]
Subtotal (95% CI)	**15**	**15**		**100%**	**1.33[0.36,4.97]**
Total events: 4 (Acyclovir), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.43(P=0.67)					
Test for subgroup differences: Chi^2=2.53, df=1 (P=0.64), I^2=0%					

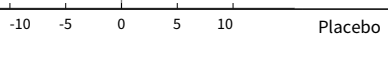


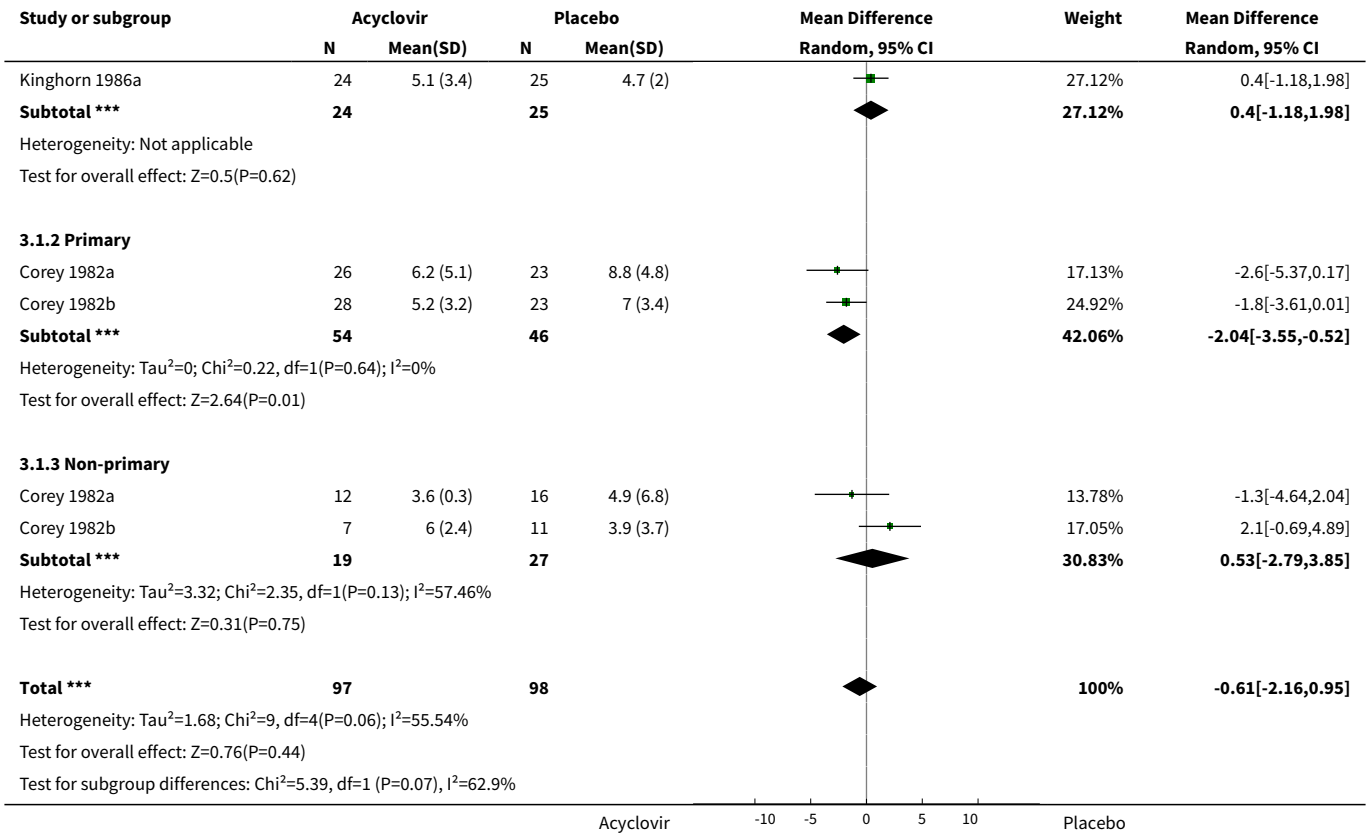
Comparison 3. Topical acyclovir versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of symptoms from onset of treatment	3	195	Mean Difference (IV, Random, 95% CI)	-0.61 [-2.16, 0.95]
1.1 All participants	1	49	Mean Difference (IV, Random, 95% CI)	0.40 [-1.18, 1.98]
1.2 Primary	2	100	Mean Difference (IV, Random, 95% CI)	-2.04 [-3.55, -0.52]
1.3 Non-primary	2	46	Mean Difference (IV, Random, 95% CI)	0.53 [-2.79, 3.85]
2 Duration of symptoms from onset of treatment by gender	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Women	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Duration of lesions from onset of treatment by antibody status	3	195	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-2.15, 0.42]
3.1 All participants	1	49	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.33, 1.73]
3.2 Primary	2	100	Mean Difference (IV, Fixed, 95% CI)	-4.09 [-6.92, -1.25]
3.3 Non-primary	2	46	Mean Difference (IV, Fixed, 95% CI)	-1.91 [-6.27, 2.46]
4 Duration of lesions from onset of treatment by gender	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Women	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Pain with topical application	3	247	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.46, 1.20]
5.2 Rash	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.82]
5.3 Itching	1	101	Risk Ratio (M-H, Fixed, 95% CI)	2.62 [0.11, 62.78]

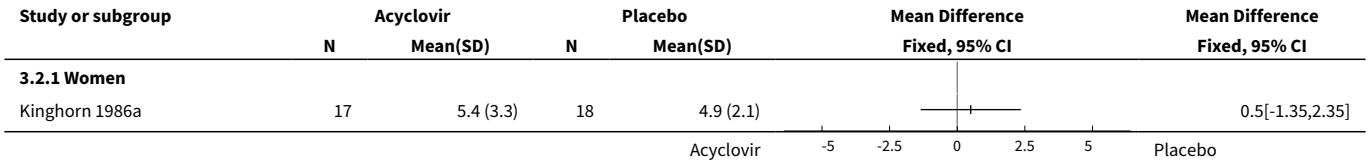
Analysis 3.1. Comparison 3 Topical acyclovir versus placebo, Outcome 1 Duration of symptoms from onset of treatment.

Study or subgroup	Acyclovir N	Acyclovir Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 All participants							

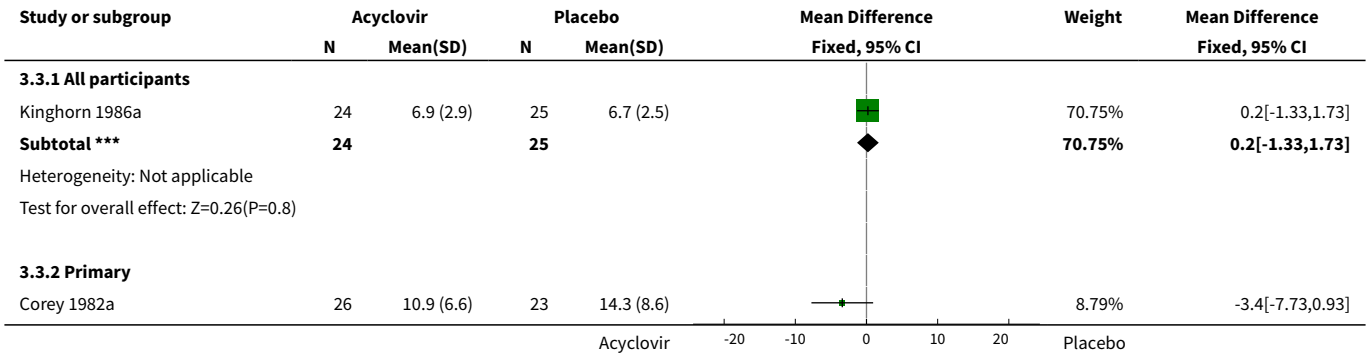


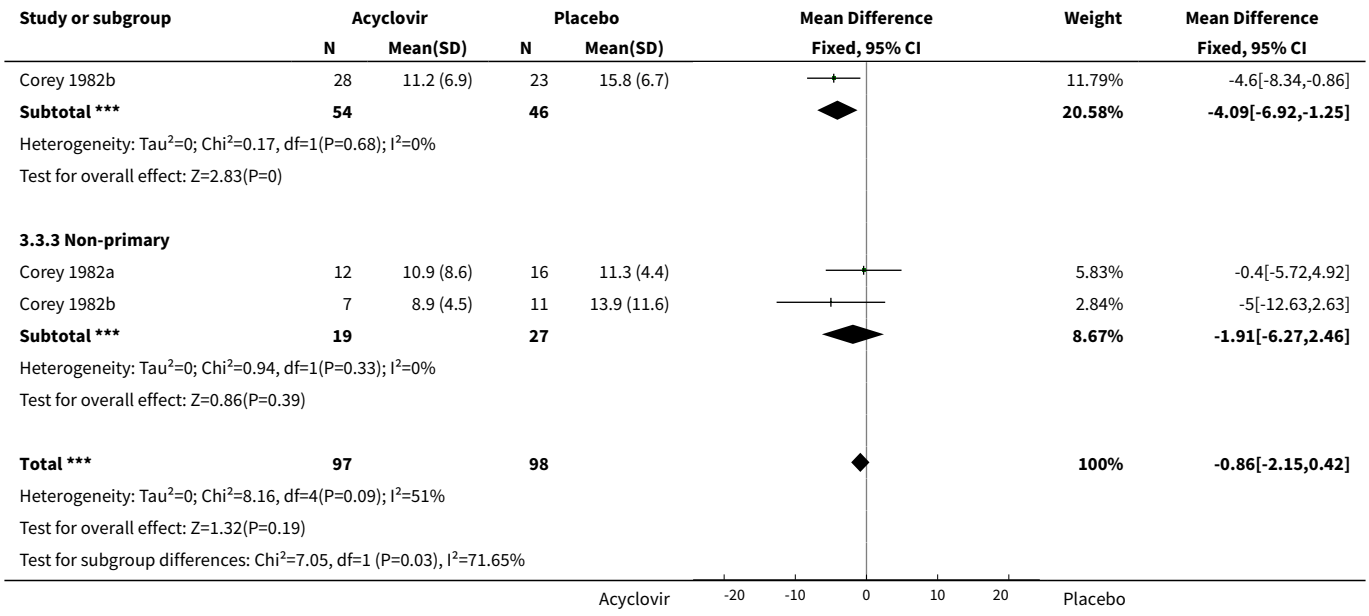


Analysis 3.2. Comparison 3 Topical acyclovir versus placebo, Outcome 2 Duration of symptoms from onset of treatment by gender.

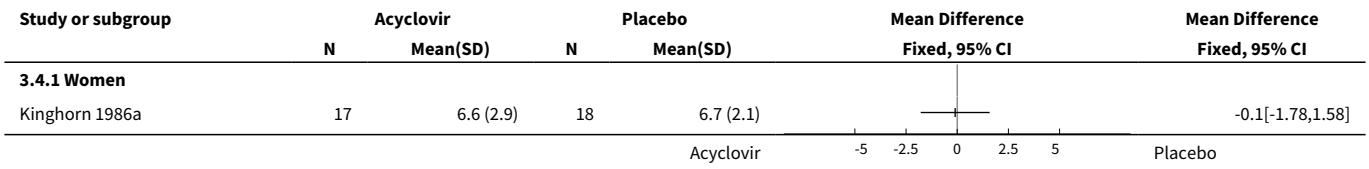


Analysis 3.3. Comparison 3 Topical acyclovir versus placebo, Outcome 3 Duration of lesions from onset of treatment by antibody status.

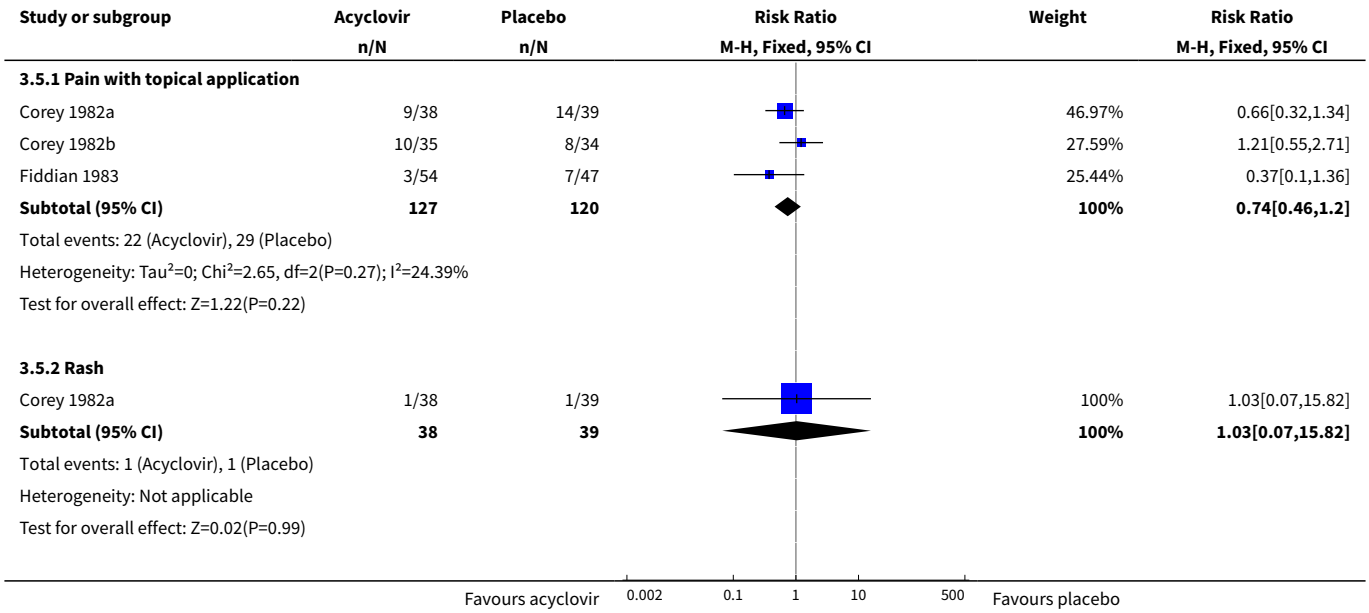


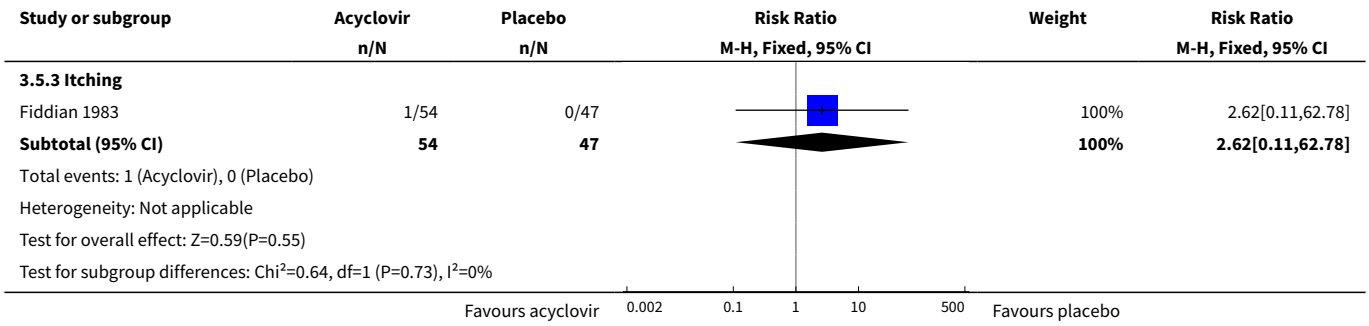


Analysis 3.4. Comparison 3 Topical acyclovir versus placebo, Outcome 4 Duration of lesions from onset of treatment by gender.



Analysis 3.5. Comparison 3 Topical acyclovir versus placebo, Outcome 5 Adverse events.

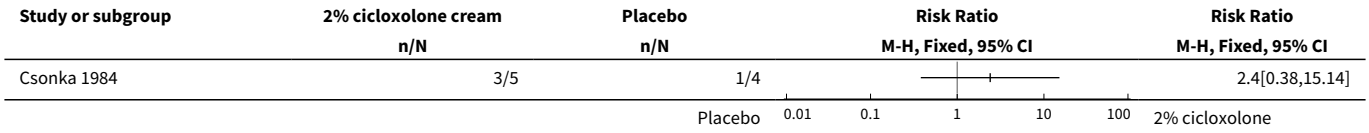




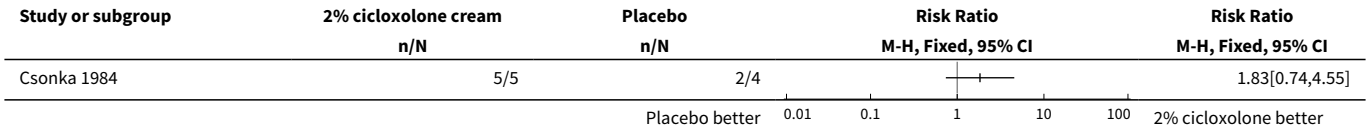
Comparison 4. Topical 2% cicloxolone cream versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom-free by end of 5 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Symptom-free by end of 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Lesion-free by end of 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Lesion-free by end of 5 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Topical 2% cicloxolone cream versus placebo, Outcome 1 Symptom-free by end of 5 days.

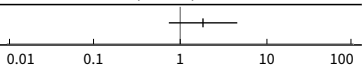


Analysis 4.2. Comparison 4 Topical 2% cicloxolone cream versus placebo, Outcome 2 Symptom-free by end of 7 days.



Analysis 4.3. Comparison 4 Topical 2% cicloxolone cream versus placebo, Outcome 3 Lesion-free by end of 7 days.

Study or subgroup	2% cicloxolone cream n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	5/5	2/4		1.83[0.74,4.55]



Analysis 4.4. Comparison 4 Topical 2% cicloxolone cream versus placebo, Outcome 4 Lesion-free by end of 5 days.

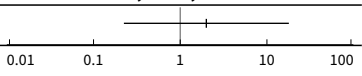
Study or subgroup	2% cicloxolone cream n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	2/5	0/4		4.17[0.25,68.16]

Comparison 5. Topical carbenoxolone sodium cream versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom-free by end of 5 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Symptom-free by end of 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Lesion-free by end of 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Lesion-free by end of 5 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

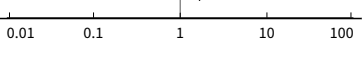
Analysis 5.1. Comparison 5 Topical carbenoxolone sodium cream versus placebo, Outcome 1 Symptom-free by end of 5 days.

Study or subgroup	Carbenoxolone cream n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	1/2	1/4		2[0.22,17.89]



Analysis 5.2. Comparison 5 Topical carbenoxolone sodium cream versus placebo, Outcome 2 Symptom-free by end of 7 days.

Study or subgroup	Carbenoxolone cream n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	2/2	2/4		1.67[0.61,4.59]



Analysis 5.3. Comparison 5 Topical carbenoxolone sodium cream versus placebo, Outcome 3 Lesion-free by end of 7 days.

Study or subgroup	Carbenoxolone cream n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	2/2	2/4		1.67[0.61,4.59]

Placebo better 0.01 0.1 1 10 100 Carbenoxolone better

Analysis 5.4. Comparison 5 Topical carbenoxolone sodium cream versus placebo, Outcome 4 Lesion-free by end of 5 days.

Study or subgroup	Carbenoxolone cream n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	2/2	0/4		8.33[0.57,121.28]

Placebo better 0.01 0.1 1 10 100 Carbenoxolone better

Comparison 6. Topical tromantadine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom and lesion-free by end of 3 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Symptom and lesion-free by end of 6 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Symptom and lesion-free by end of 9 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Symptom and lesion-free by end of 12 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

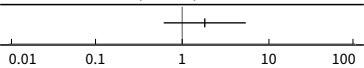
Analysis 6.1. Comparison 6 Topical tromantadine versus placebo, Outcome 1 Symptom and lesion-free by end of 3 days.

Study or subgroup	Tromatidine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Altomare 1985	3/11	0/10		6.42[0.37,110.71]

Favours placebo 0.002 0.1 1 10 500 Favours tromantadine

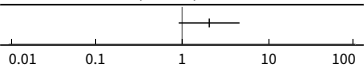
Analysis 6.2. Comparison 6 Topical tromantadine versus placebo, Outcome 2 Symptom and lesion-free by end of 6 days.

Study or subgroup	Tromatidine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Altomare 1985	6/11	3/10		1.82[0.61,5.41]



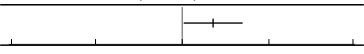
Analysis 6.3. Comparison 6 Topical tromantadine versus placebo, Outcome 3 Symptom and lesion-free by end of 9 days.

Study or subgroup	Tromatidine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Altomare 1985	9/11	4/10		2.05[0.91,4.59]



Analysis 6.4. Comparison 6 Topical tromantadine versus placebo, Outcome 4 Symptom and lesion-free by end of 12 days.

Study or subgroup	Tromatidine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Altomare 1985	10/11	4/10		2.27[1.04,4.97]



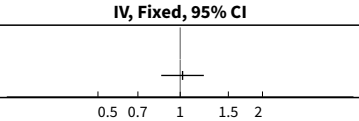
Comparison 7. Oral valaciclovir versus acyclovir

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of symptoms from onset of treatment	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
1.1 Valacyclovir versus acyclovir	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Duration of symptoms from onset of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Valaciclovir versus acyclovir	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nausea	2	671	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.65]
3.2 Headache	2	671	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.82, 1.93]
4 Duration of lesions from onset of treatment	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Valaciclovir versus acyclovir	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]

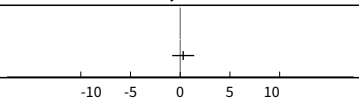
Analysis 7.1. Comparison 7 Oral valaciclovir versus acyclovir, Outcome 1 Duration of symptoms from onset of treatment.

Study or subgroup	Valaciclovir N	Acyclovir N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
7.1.1 Valacyclovir versus acyclovir					
Fife 1997	323	320	0 (0.092)		1.02[0.85,1.22]



Analysis 7.2. Comparison 7 Oral valaciclovir versus acyclovir, Outcome 2 Duration of symptoms from onset of treatment.

Study or subgroup	Valaciclovir N	Valaciclovir Mean(SD)	Acyclovir N	Acyclovir Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
7.2.1 Valaciclovir versus acyclovir						
Lai 2000	13	5.6 (1.7)	15	5.3 (1.2)		0.3[-0.81,1.41]

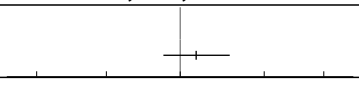


Analysis 7.3. Comparison 7 Oral valaciclovir versus acyclovir, Outcome 3 Adverse events.

Study or subgroup	Valaciclovir n/N	Acyclovir n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.3.1 Nausea					
Fife 1997	18/323	20/320		95.58%	0.89[0.48,1.65]
Lai 2000	1/13	1/15		4.42%	1.15[0.08,16.67]
Subtotal (95% CI)	**336**	**335**		**100%**	**0.9[0.49,1.65]**
Total events: 19 (Valaciclovir), 21 (Acyclovir)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					
7.3.2 Headache					
Fife 1997	41/323	33/320		98.61%	1.23[0.8,1.9]
Lai 2000	1/13	0/15		1.39%	3.43[0.15,77.58]
Subtotal (95% CI)	**336**	**335**		**100%**	**1.26[0.82,1.93]**
Total events: 42 (Valaciclovir), 33 (Acyclovir)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=1.07(P=0.29)					
Test for subgroup differences: Chi^2=0.79, df=1 (P=0.37), I^2=0%					

Analysis 7.4. Comparison 7 Oral valaciclovir versus acyclovir, Outcome 4 Duration of lesions from onset of treatment.

Study or subgroup	Valaciclovir N	Acyclovir N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
7.4.1 Valaciclovir versus acyclovir					
Fife 1997	323	320	0.1 (0.082)		1.08[0.92,1.27]

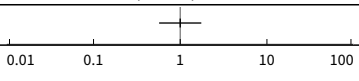


Comparison 8. Topical carbenoxolone sodium versus topical cicloxolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom-free by end of 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Lesion-free by end of 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

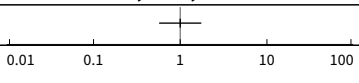
Analysis 8.1. Comparison 8 Topical carbenoxolone sodium versus topical cicloxolone, Outcome 1 Symptom-free by end of 7 days.

Study or subgroup	Carbenoxolone cream n/N	2% cicloxolone cream n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	2/2	5/5		1[0.57,1.75]



Analysis 8.2. Comparison 8 Topical carbenoxolone sodium versus topical cicloxolone, Outcome 2 Lesion-free by end of 7 days.

Study or subgroup	Carbenoxolone cream n/N	2% cicloxolone cream n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Csonka 1984	2/2	5/5		1[0.57,1.75]



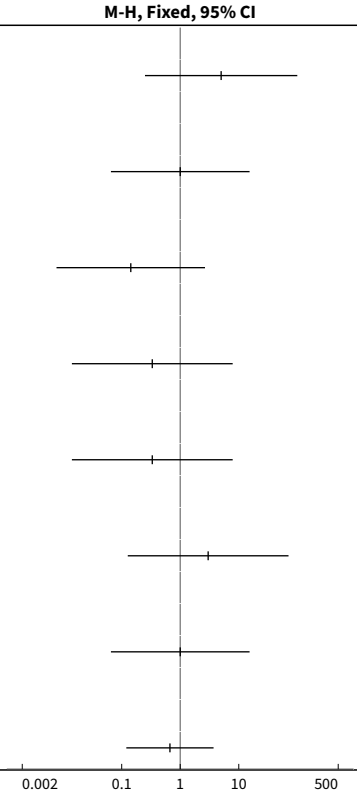
Comparison 9. Oral acyclovir regimen comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long versus standard course: adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Constipation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Increase in appetite	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Bells palsy	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Slight white cell count decrease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Persistent bilirubin elevation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.8 Slight transient bilirubin elevation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 HIgh versus low dose: adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Drug toxicity	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Oral acyclovir regimen comparisons, Outcome 1 Long versus standard course: adverse events.

Study or subgroup	Long course n/N	Standard course n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
9.1.1 Constipation				
Mindel 1986	2/30	0/30		5[0.25,99.95]
9.1.2 Nausea				
Mindel 1986	1/30	1/30		1[0.07,15.26]
9.1.3 Diarrhoea				
Mindel 1986	0/30	3/30		0.14[0.01,2.65]
9.1.4 Increase in appetite				
Mindel 1986	0/30	1/30		0.33[0.01,7.87]
9.1.5 Bells palsy				
Mindel 1986	0/30	1/30		0.33[0.01,7.87]
9.1.6 Slight white cell count decrease				
Mindel 1986	1/30	0/30		3[0.13,70.83]
9.1.7 Persistent bilirubin elevation				
Mindel 1986	1/30	1/30		1[0.07,15.26]
9.1.8 Slight transient bilirubin elevation				
Mindel 1986	2/30	3/30		0.67[0.12,3.71]



Analysis 9.2. Comparison 9 Oral acyclovir regimen comparisons, Outcome 2 HIgh versus low dose: adverse events.

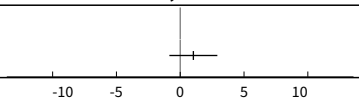
Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
9.2.1 Drug toxicity				
Wald 1994	7/88	0/41		7.08[0.41,121.05]

Comparison 10. Topical acyclovir versus intramuscular interferon

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of symptoms from onset of treatment by antibody status	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 All participants	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Visual disturbance	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Dizziness	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Anorexia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Sweating	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 Chills	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.11 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.12 Myalgia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.13 Neutropenia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Duration of lesions from onset of treatment by antibody status	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 All participants	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

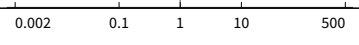
Analysis 10.1. Comparison 10 Topical acyclovir versus intramuscular interferon, Outcome 1 Duration of symptoms from onset of treatment by antibody status.

Study or subgroup	Topical acyclovir N	Topical acyclovir Mean(SD)	IM interferon N	IM interferon Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.1.1 All participants						
Levin 1989	53	6.3 (5.7)	52	5.3 (4)		1.03[-0.85,2.91]

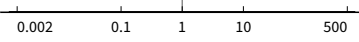


Analysis 10.2. Comparison 10 Topical acyclovir versus intramuscular interferon, Outcome 2 Adverse events.

Study or subgroup	IM interferon n/N	Topical acyclovir n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
10.2.1 Visual disturbance				
Levin 1989	17/58	7/66		2.76[1.23,6.19]
10.2.2 Dizziness				
Levin 1989	12/58	2/66		6.83[1.59,29.25]
10.2.3 Diarrhoea				
Levin 1989	11/58	13/66		0.96[0.47,1.98]
10.2.4 Nausea				
Levin 1989	27/58	17/66		1.81[1.1,2.96]
10.2.5 Vomiting				
Levin 1989	11/58	5/66		2.5[0.92,6.78]
10.2.6 Anorexia				
Levin 1989	29/58	19/66		1.74[1.1,2.75]
10.2.7 Sweating				
Levin 1989	8/58	0/66		19.31[1.14,327.34]
10.2.8 Fever				
Levin 1989	47/58	14/66		3.82[2.36,6.18]
10.2.9 Fatigue				
Levin 1989	43/58	34/66		1.44[1.09,1.9]
10.2.10 Chills				
Levin 1989	44/58	16/66		3.13[1.99,4.91]
10.2.11 Headache				
Levin 1989	40/58	29/66		1.57[1.14,2.17]
10.2.12 Myalgia				
Levin 1989	46/58	30/66		1.74[1.3,2.34]
10.2.13 Neutropenia				

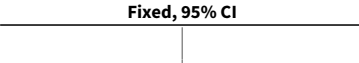


Study or subgroup	IM interferon n/N	Topical acyclovir n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Levin 1989	25/58	5/66		5.69[2.33,13.9]



Analysis 10.3. Comparison 10 Topical acyclovir versus intramuscular interferon, Outcome 3 Duration of lesions from onset of treatment by antibody status.

Study or subgroup	Topical acyclovir N	Topical acyclovir Mean(SD)	IM interferon N	IM interferon Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.3.1 All participants						
Levin 1989	53	12.6 (5.6)	52	11 (4.6)		1.58[-0.38,3.54]



Comparison 11. Subcutaneous interferon versus placebo

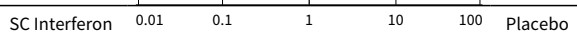
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of symptoms from onset of treatment	1	31	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Men	1	13	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Women	1	18	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Chills	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Myalgia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Anorexia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 Neutropenia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

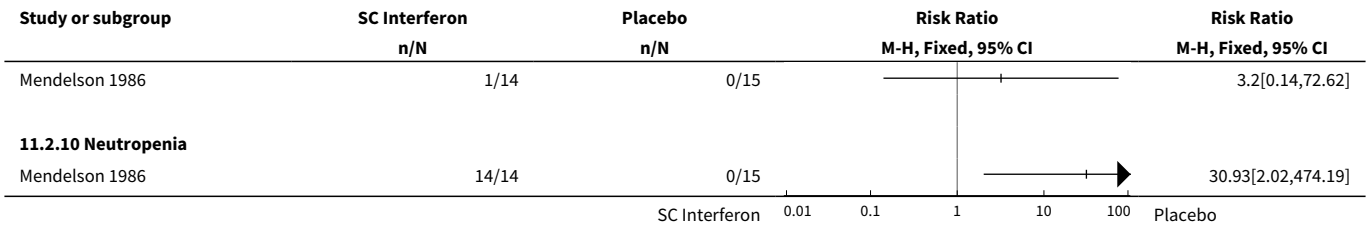
Analysis 11.1. Comparison 11 Subcutaneous interferon versus placebo, Outcome 1 Duration of symptoms from onset of treatment.

Study or subgroup	SC Interferon N	SC Interferon Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.1.1 Men							
Mendelson 1986	6	5.3 (0)	7	4.7 (0)			Not estimable
Subtotal ***	**6**		**7**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
11.1.2 Women							
Mendelson 1986	10	4.4 (0)	8	3.6 (0)			Not estimable
Subtotal ***	**10**		**8**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**16**		**15**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Analysis 11.2. Comparison 11 Subcutaneous interferon versus placebo, Outcome 2 Adverse events.

Study or subgroup	SC Interferon n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
11.2.1 Fever				
Mendelson 1986	12/14	1/15		12.86[1.91,86.44]
11.2.2 Headache				
Mendelson 1986	10/14	3/15		3.57[1.23,10.36]
11.2.3 Chills				
Mendelson 1986	11/14	2/15		5.89[1.58,22.03]
11.2.4 Myalgia				
Mendelson 1986	7/14	3/15		2.5[0.8,7.81]
11.2.5 Nausea				
Mendelson 1986	5/14	2/15		2.68[0.62,11.64]
11.2.6 Vomiting				
Mendelson 1986	3/14	1/15		3.21[0.38,27.4]
11.2.7 Fatigue				
Mendelson 1986	8/14	5/15		1.71[0.73,4]
11.2.8 Anorexia				
Mendelson 1986	8/14	1/15		8.57[1.22,60.07]
11.2.9 Diarrhoea				

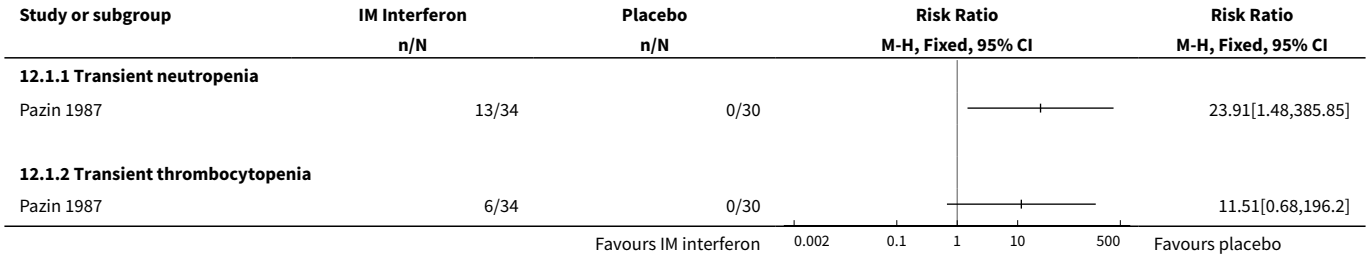




Comparison 12. Intramuscular interferon versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Transient neutropenia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Transient thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 Intramuscular interferon versus placebo, Outcome 1 Adverse events.

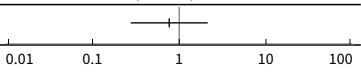


Comparison 13. High dose famciclovir versus low dose famciclovir

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants symptoms resolved at day 5	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Lesions not visible at day 5	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 High dose famciclovir versus low dose famciclovir, Outcome 1 Participants symptoms resolved at day 5.

Study or subgroup	High dose n/N	low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Niimura 1996	5/27	7/29		0.77[0.28,2.13]



Analysis 13.2. Comparison 13 High dose famciclovir versus low dose famciclovir, Outcome 2 Lesions not visible at day 5.

Study or subgroup	High dose n/N	low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Niimura 1996	7/20	10/29		1.01[0.47,2.21]

ADDITIONAL TABLES

Table 1. Number of days from onset of symptoms that patients were included

Time	Less than 24 hrs	Less than 2 days	Less than 3 days	Less than 4 days	Less than 5 days	Less than 6 days	Less than 7 days	Less than 8 days	Did not state
Studies of oral antivirals			Fife 1997		Lai 2000; Mindel 1986; Nilsen 1982; Wald 1994	Bryson 1983; Kinghorn 1986b; Mertz 1984			Niimura 1996 included from day 2, 3, 4, 5, 6, 7 or more, but subgrouped data of results was not available
Studies of topical antivirals					Fiddian 1983	Corey 1982a; Corey 1982b; Kinghorn 1986a			
Studies of intravenous antivirals						Mindel 1982 Severe GH	Corey 1983; Peacock 1988		
Studies of topical interferon									Batcheler 1986
Studies of IM/SC interferon			Pazin 1987 (IM)	Levin 1989 (IM)	Mendelson 1986 (SC)				
Studies of adenosine arabinoside		Adams 1976							
Studies of topical carbenoxolone versus topical cicloxone					Csonka 1984				
Studies of ribavirin			Zavala 1988						
Studies of topical idoxuridine versus dimethyl sulfoxide								Silvestri 1982	
Studies of oral inosine pranobex					Mindel 1987				

Table 1. Number of days from onset of symptoms that patients were included *(Continued)*

Studies of topical tromantadine	Altomare 1985

GH: genital herpes
IM: intramuscular
SC: subcutaneous

Table 2. Medians: oral acyclovir versus placebo

		Acyclovir		Placebo			
Outcome	**Study**	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**P value**	**Favours intervention**
Duration of symptoms from onset of treatment	Nilsen 1982	4	17	9	14	< 0.05	✓
Duration of symptoms from onset of treatment by antibody status							
Primary	Mertz 1984	5	52	7	49	< 0.05	✓
Non-primary	Mertz 1984	2	9	4	15	> 0.1	#
Duration of symptoms from onset of treatment by gender							
Females	Nilsen 1982	5	10	8	7	NS	#
Males	Nilsen 1982	3	7	9	7	< 0.05	✓
Duration of lesions from onset of treatment	Nilsen 1982	6	17	11	14	< 0.01	✓
Duration of lesions from onset of treatment by antibody status							
Primary	Mertz 1984	12	61	16	58	< 0.01	✓
Non-primary	Mertz 1984	9	12	13	19	> 0.1	#

Table 2. Medians: oral acyclovir versus placebo *(Continued)*

Duration of lesions from onset of treatment by gender							
Females	Nilsen 1982	4.5	10	6	7	< 0.05	✓
Males	Nilsen 1982	7	7	11	7	0.06	#
Time to recurrence							#
Participants with 4-9 month follow-up	Bryson 1983	94	Unclear	101	Unclear	NS	#
HSV-2 group	Mertz 1984	71	Unclear	108	Unclear	NS	#

Mertz 1984: Duration of symptoms refers specifically to pain
HSV-2: herpes simplex virus type 2
NS: not statistically significant
✓: favours intervention
#: does not favour intervention

Table 3. Mean: oral ribavirin versus placebo

		Oral ribavirin		Placebo		
Outcome	**Study**	**Mean (days)**	**No. participants**	**Mean (days)**	**No. participants**	**Favours intervention**
Duration of symptoms from the onset of treatment	Zavala 1988	5.7	30	15.5	30	✓

✓: favours intervention

Table 4. Medians: intravenous acyclovir versus placebo

		Acyclovir		Placebo			
Outcome	**Study**	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**P value**	**Favours intervention**
Duration of symptoms from onset of treatment - all							
	Mindel 1982	6.5	15	8.5	15	< 0.05	✓
	Peacock 1988	4.3	42	4.8	40	0.019	✓
	Corey 1983	4	15	7	16	0.17	#
Duration of symptoms from onset of treatment by antibody status							
Primary	Mindel 1982	6.3	12	8.8	8	NS	#
	Peacock 1988	4.2		10.6		0.009	✓
	Corey 1983	3	14	7	13	0.17	#
Non-primary	Peacock 1988	4.4		3.8		0.55	✓
Duration of symptoms from onset of treatment by gender							
Female	Mindel 1982	6.8	12	7.3	12	NS	#
Duration of lesions from onset of treatment							
	Mindel 1982	7.0	15	14.0	15	< 0.001	✓
	Peacock 1988	8.4	42	11.5	40	0.02	✓
	Corey 1983	9	15	21	16	0.002	✓
Duration of lesions from onset of treatment by antibody status							

Table 4. Medians: intravenous acyclovir versus placebo *(Continued)*

Primary	Mindel 1982	9.0	12	15.0	8	< 0.05	✓
	Peacock 1988	8.3	22	14.2	22	0.015	✓
	Corey 1983	9	14	21	13	0.007	✓
Non-primary	Peacock 1988	8.4	20	8.2	18	NS	#
Duration of lesions from onset of treatment by gender							
Female	Mindel 1982	7.0	12	12.5	12	< 0.05	✓
Time to first recurrence by HSV type							
HSV-1	Corey 1983 + Mindel 1982	279	7	184	7	0.4	#
HSV-2	Corey 1983 + Mindel 1982	64	23	74	23	0.4	#

Duration of symptoms: Peacock 1988 refers specifically to pain; Corey 1983 refers to constitutional symptoms
HSV-1: herpes simplex virus type 1
HSV-2: herpes simplex virus type 2
NS: not statistically significant
✓: favours intervention
#: does not favour intervention

Table 5. Medians: topical acyclovir versus placebo

		Topical acyclovir		Topical placebo			
Outcome	**Study**	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**P value**	**Favours intervention**
Duration of symptoms from onset of treatment - all							
	Fiddian 1983	5	54	8	47	0.01	✓

Table 5. Medians: topical acyclovir versus placebo *(Continued)*

Duration of symptoms from onset of treatment by gender							
Females	Fiddian 1983	6	35	9	31	< 0.05	✓
Males	Fiddian 1983	3.5	19	6	16	> 0.1	#
Duration of lesions from onset of treatment - all							
	Fiddian 1983	8	54	13	47	0.01	✓
Duration of lesions from onset of treatment by gender							
Females	Fiddian 1983	8	35	13	31	< 0.001	✓
Males	Fiddian 1983	8	19	11	16	< 0.01	✓
Time to first recurrence							
	Corey 1982a	116		116			#
	Corey 1982b	79		79			#

✓: favours intervention
#: does not favour intervention

Table 6. Mean: adenosine arabinoside versus placebo

		Adenine arabinoside		Placebo		No treatment		Untreated (no contraception)		
	Study	**Mean (days)**	**No. participants**	**Mean (days)**	**No. participants**	**Mean (days)**	**No. participants**	**Mean (days)**	**No. participants**	**Favours intervention**
Duration of symptoms from onset of treatment by gender										
Females	Adams 1976	10.4	8	6.8	10	8.8	4	7.0	5	#

Table 6. Mean: adenosine arabinoside versus placebo *(Continued)*

Males	Adams 1976	7.8	9	6.3	9	6.5	4			#
Duration of lesions from onset of treatment by gender										
Females	Adams 1976	16.1	8	11	10	10	4	13.6	5	#
Males	Adams 1976	11.9	9	13.1	9	11.5	4			#

#: does not favour intervention

Table 7. Mean: topical 30% idoxuridine in dimethyl sulfoxide versus control

		Topical 30% idoxuridine		Control*		
Outcome	**Study**	**Mean (days)**	**No. participants**	**Mean (days)**	**No. participants**	**Favours intervention**
Duration of symptoms from the onset of treatment - all						
	Silvestri 1982	10.7	9	12.9	23	#
Duration of lesions from the onset of treatment - all						
	Silvestri 1982	19.6	9	17.9	23	#
Adverse effects		**Events**	**No. Participants**	**Events**	**No. participants**	
Burning on application	Silvestri 1982	5	9	6	23	#

*Control: either dimethyl sulfoxide alone or saline alone
#: does not favour intervention

Table 8. Medians: oral acyclovir versus inosine pranobex versus both

		Acyclovir		Inosine pranobex		Both			
	Study	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**P value**	**Favours Acyclovir**
Duration of symptoms from onset of treatment - all									
	Mindel 1987	7 (range 3 to 19)	24	8 (range 4 to 23)	28	7 (range 3 to 19)	25	Acyclovir versus inosine: NS Acyclovir versus both: NS	#
Duration of symptoms from onset of treatment by gender									
Females	Mindel 1987	7 (range 3 to 19)		9.5 (range 4 to 23)		7 (range 3 to 19)		Acyclovir versus inosine: P < 0.05 Acyclovir versus both: NS	✓
Duration of lesions from onset of treatment - all									
	Mindel 1987	9 (range 4 to 24)	24	13 (range 1 to 26)	28	9 (range 5 to 18)	25	Acyclovir versus inosine: P < 0.05 Acyclovir versus both: NS	✓
Duration of lesions from onset of treatment by gender									
Females	Mindel 1987	9.5 (range 4 to 24)		13 (range 1 to 26)		9 (range 5 to 18)		Acyclovir versus inosine: NS Acyclovir versus both: NS	#
Time to recurrence									

Table 8. Medians: oral acyclovir versus inosine pranobex versus both *(Continued)*

	Mindel 1987	187.4	142.5	132.7	NS	#

NS: not statistically significant
✓: favours acyclovir
#: does not favour acyclovir

Table 9. Medians: oral acyclovir long course versus standard course

		Long course acyclovir		Short course acyclovir			
Outcome	**Study**	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**P value**	**Favours long course acyclovir**
Duration of symptoms from onset of treatment by gender							
Female	Mindel 1986	11 (range 1 to 31)	30	11 (range 2 to 28)	30	NS	#
Duration of lesions from onset of treatment by gender							
Female	Mindel 1986	11 (range 5 to 34)	30	11 (range 5 to 32)	30	NS	#

NS: not statistically significant
#: does not favour long course acyclovir

Table 10. Medians: oral acyclovir high dose versus standard dose

		High dose acyclovir		Low dose acyclovir			
Outcome	**Study**	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**P value**	**Favours high dose acyclovir**
Duration of symptoms from onset of treatment - all							
	Wald 1994	7 (range 5 to 10)	59	9 (range 7 to 12)	28	NS	#

Table 10. Medians: oral acyclovir high dose versus standard dose *(Continued)*

Duration of lesions from onset of treatment - all							
	Wald 1994	11 (range 8 to 14)	59	10 (range 7 to 11)	28	NS	#
Time to recurrence - all							
	Wald 1994	45 (range 20 to 128)	See footnote	53 (range 11 to 196)	See footnote	NS	#

Recurrence occurred in 80% of participants
NS: not statistically significant
#: does not favour high dose acyclovir

Table 11. Mean: topical interferon versus placebo

		Topical interferon		Placebo		
Outcome	**Study**	**Mean (days)**	**No. participants**	**Mean (days)**	**No. participants**	**Favours intervention**
Duration of symptoms from the onset of treatment						
	Batcheler 1986	7.25	12	6.33	18	X
Duration of lesions from the onset of treatment						
	Batcheler 1986	8.06	16	6.52	19	X

✓: favours intervention
#: does not favour intervention

Table 12. Medians: intramuscular interferon versus placebo

		Intramuscular interferon		Placebo			
Outcome	**Study**	**Median (days)**	**No. participants**	**Median (days)**	**No. participants**	**P value**	**Favours intervention**
Duration of lesions from onset of treatment - women							
	Pazin 1987	16	34	22	30	P < 0.05 for days 18 to 20 only	#

#: does not favour intervention

APPENDICES

Appendix 1. Electronic search strategies

Medline (Ovid)

(02/04/2016)

1 exp Herpes Genitalis/ (4275)

2 herpe$.tw. (76899)

3 exp Herpes Simplex/ (22486)

4 HHV.tw. (4409)

5 HSV.tw. (21157)

6 exp Simplexvirus/ (28145)

7 simplexviru$.tw. (30)

8 (marmoset adj5 virus$).tw. (94)

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (86193)

10 anal.tw. (29839)

11 anogenital.tw. (3386)

12 anorectal.tw. (8969)

13 genital$.tw. (56334)

14 penile.tw. (17150)

15 penis.tw. (12429)

16 perianal.tw. (5491)

17 rectal.tw. (69420)

18 vaginal.tw. (72767)

19 venereal.tw. (5408)

20 vulva$.tw. (13904)

21 vulvovaginal.tw. (1712)

22 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (257408)

23 9 and 22 (6144)

24 exp Herpesvirus 2, Human/ (3711)

25 herpesvirus 2.tw. (413)

26 herpesvirus II.tw. (9)

27 (herpes adj5 herpe$).tw. (52909)

28 (herpes adj5 II).tw. (373)

29 HHV 2.tw. (22)

30 HHV2.tw. (5)

31 HSV 2.tw. (5319)

32 HSV2.tw. (323)

33 1 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (55351)

34 exp Antiviral Agents/ (303715)

35 antivir$.tw. (63908)

36 anti vir$.tw. (5577)

37 viral inhibitor.tw. (100)

38 virus repressor.tw. (2)

39 virucid$.tw. (1215)

40 vir?static.tw. (313)

41 exp Acyclovir/ (12863)

42 ac?clovir.tw. (7599)

43 valac?clovir.tw. (972)

44 famciclovir.tw. (591)

45 exp Ganciclovir/ (5623)

46 ganc?clovir.tw. (6177)

47 cidof?vir.tw. (1471)

48 exp Foscarnet/ (1484)

49 foscarnet.tw. (1547)

50 exp Interferons/ (119762)

51 interferon$.tw. (127762)

52 IFN.tw. (96393)

53 imiquimod.tw. (2111)

54 resiquimod.tw. (159)

55 exp Biological Factors/ (2841008)

56 (biologic$ adj5 agent$).tw. (12274)

57 (biologic$ adj5 product$).tw. (8626)

58 (natural adj5 product$).tw. (26380)

59 natural compound$.tw. (4368)

60 Clinacanthus nutans.tw. (25)

61 exp Lysine/ (35397)

62 lysine.tw. (55146)

63 exp Ascorbic Acid/ (38528)

64 ascorb$.tw. (38553)

65 xyloascorbic acid.tw. (3)

66 (vitam$ adj5 C).tw. (21237)

67 antiscorbutic vitamin.tw. (3)

68 exp Vitamin E/ (29617)

69 vitamin E.tw. (24099)

70 alpha tocopher$.tw. (14687)

71 alphatocopher$.tw. (39)

72 exp Zinc/ (52222)

73 zinc$.tw. (90668)

74 exp Lithium/ (20694)

75 lithium.tw. (34282)

76 exp Adenosine Monophosphate/ (9325)

77 adenosine.tw. (93521)

78 adenine.tw. (37098)

79 AMP.tw. (57857)

80 adenylic acid.tw. (531)

81 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 (3475012)

82 randomized controlled trial.pt. (411144)

83 controlled clinical trial.pt. (90371)

84 randomized.ab. (340883)

85 placebo.ab. (168016)

86 clinical trials as topic.sh. (175597)

87 randomly.ab. (245501)

88 trial.ti. (148072)

89 82 or 83 or 84 or 85 or 86 or 87 or 88 (1005320)

90 exp animals/ not humans.sh. (4210486)

91 89 not 90 (925788)

92 33 and 81 and 91 (1408)

CENTRAL (Ovid platform)

(02/04/2016)

1 exp Herpes Genitalis/ (333)

2 herpe$.tw. (2144)

3 exp Herpes Simplex/ (772)

4 HHV.tw. (41)

5 HSV.tw. (439)

6 exp Simplexvirus/ (310)

7 simplexviru$.tw. (0)

8 (marmoset adj5 virus$).tw. (0)

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (2293)

10 anal.tw. (1756)

11 anogenital.tw. (110)

12 anorectal.tw. (504)

13 genital$.tw. (1804)

14 penile.tw. (749)

15 penis.tw. (213)

16 perianal.tw. (324)

17 rectal.tw. (5243)

18 vaginal.tw. (7394)

19 venereal.tw. (35)

20 vulva$.tw. (359)

21 vulvovaginal.tw. (238)

22 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (16670)

23 9 and 22 (504)

24 exp Herpesvirus 2, Human/ (145)

25 herpesvirus 2.tw. (0)

26 herpesvirus II.tw. (0)

27 (herpes adj5 herpe$).tw. (1866)

28 (herpes adj5 II).tw. (12)

29 HHV 2.tw. (1)

30 HHV2.tw. (0)

31 HSV 2.tw. (220)

32 HSV2.tw. (12)

33 1 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (1937)

34 exp Antiviral Agents/ (12340)

35 antivir$.tw. (2477)

36 anti vir$.tw. (169)

37 viral inhibitor.tw. (0)

38 virus repressor.tw. (0)

39 virucid$.tw. (21)

40 vir?static.tw. (20)

41 exp Acyclovir/ (943)

42 ac?clovir.tw. (942)

43 valac?clovir.tw. (259)

44 famciclovir.tw. (136)

45 exp Ganciclovir/ (284)

46 ganc?clovir.tw. (386)

47 cidof?vir.tw. (38)

48 exp Foscarnet/ (69)

49 foscarnet.tw. (88)

50 exp Interferons/ (4444)

51 interferon$.tw. (9130)

52 IFN.tw. (4533)

53 imiquimod.tw. (232)

54 resiquimod.tw. (12)

55 exp Biological Factors/ (50893)

56 (biologic$ adj5 agent$).tw. (297)

57 (biologic$ adj5 product$).tw. (99)

58 (natural adj5 product$).tw. (202)

59 natural compound$.tw. (35)

60 Clinacanthus nutans.tw. (3)

61 exp Lysine/ (334)

62 lysine.tw. (686)

63 exp Ascorbic Acid/ (1607)

64 ascorb$.tw. (1250)

65 xyloascorbic acid.tw. (0)

66 (vitam$ adj5 C).tw. (2365)

67 antiscorbutic vitamin.tw. (0)

68 exp Vitamin E/ (1983)

69 vitamin E.tw. (2454)

70 alpha tocopher$.tw. (1131)

71 alphatocopher$.tw. (12)

72 exp Zinc/ (1208)

73 zinc$.tw. (2957)

74 exp Lithium/ (626)

75 lithium.tw. (1756)

76 exp Adenosine Monophosphate/ (141)

77 adenosine.tw. (2254)

78 adenine.tw. (243)

79 AMP.tw. (650)

80 adenylic acid.tw. (0)

81 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 (77359)

82 33 and 81 (1156)

EMBASE.com

(02/04/2016)

#1. 'genital herpes'/exp

#2. herpe*:ab,ti

#3. 'herpes simplex'/exp

#4. 'herpes simplex virus'/exp

#5. 'herpes virus'/exp

#6. hhv:ab,ti

#7. hsv:ab,ti

#8. 'simplexvirus'/exp

#9. simplexviru*:ab,ti

#10. (marmoset NEAR/5 virus*):ab,ti

#11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12. anal:ab,ti

#13. anogenital:ab,ti

#14. anorectal:ab,ti

#15. genital*:ab,ti

#16. penile:ab,ti

#17. penis:ab,ti

#18. perianal:ab,ti

#19. rectal:ab,ti

#20. vaginal:ab,ti

#21. venereal:ab,ti

#22. vulva*:ab,ti

#23. vulvovaginal:ab,ti

#24. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#25. #11 AND #24 8,221

#26. 'herpes simplex virus 2'/exp

#27. 'herpesvirus 2':ab,ti

#28. 'herpesvirus ii':ab,ti

#29. (herpes NEAR/5 2):ab,ti

#30. (herpes NEAR/5 ii):ab,ti

#31. 'hhv 2':ab,ti

#32. hhv2:ab,ti

#33. 'hsv 2':ab,ti

#34. hsv2:ab,ti

#35. #1 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34

#36. 'antivirus agent'/exp

#37. 'antiviral therapy'/exp

#38. antivir*:ab,ti

#39. (anti NEAR/5 vir*):ab,ti

#40. 'viral inhibitor':ab,ti

#41. 'virus repressor':ab,ti

#42. virucid*:ab,ti

#43. vir?static

#44. 'aciclovir'/exp

#45. ac?clovir

#46. 'valaciclovir'/exp

#47. valac?clovir

#48. 'famciclovir'/exp

#49. famciclovir:ab,ti

#50. 'ganciclovir'/exp

#51. ganc?clovir

#52. 'cidofovir'/exp

#53. cidof?vir

#54. 'foscarnet'/exp

#55. foscarnet:ab,ti

#56. 'interferon'/exp

#57. interferon*:ab,ti

#58. ifn:ab,ti

#59. 'imiquimod'/exp

#60. imiquimod:ab,ti

#61. resiquimod:ab,ti

#62. 'biological product'/exp

#63. (biologic* NEAR/5 agent*):ab,ti

#64. (biologic* NEAR/5 product*):ab,ti

#65. 'natural product'/exp

#66. (natural NEAR/5 product*):ab,ti

#67. (natural NEAR/5 compound*):ab,ti

#68. 'clinacanthus nutans':ab,ti

#69. 'lysine'/exp

#70. lysine:ab,ti

#71. 'ascorbic acid'/exp

#72. ascorb*:ab,ti

#73. 'xyloascorbic acid':ab,ti

#74. (vitam* NEAR/5 c):ab,ti

#75. 'antiscorbutic vitamin':ab,ti

#76. 'alpha tocopherol'/exp

#77. 'vitamin e':ab,ti

#78. (alpha NEAR/5 tocopher*):ab,ti

#79. alphatocopher*:ab,ti

#80. 'zinc'/exp

#81. zinc*:ab,ti

#82. 'lithium'/exp

#83. lithium:ab,ti

#84. 'adenosine phosphate'/exp

#85. adenosine:ab,ti

#86. adenine:ab,ti

#87. amp:ab,ti

#88. 'adenylic acid':ab,ti

#89. #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88

#90. 'randomized controlled trial'/exp

#91. 'single blind procedure'/exp

#92. 'double blind procedure'/exp

#93. 'crossover procedure'/exp

#94. . #90 OR #91 OR #92 OR #93

#95. random*:ab,ti

#96. placebo*:ab,ti

#97. allocat*:ab,ti

#98. crossover*:ab,ti

#99. 'cross over':ab,ti

#100.trial:ti

#101.(doubl* NEXT/1 blind*):ab,ti

#102. #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101

#103. #94 OR #102

#104.'animal'/de

#105.'animal experiment'/de

#106.'nonhuman'/de

#107. #104 OR #105 OR #106

#108.'human'/de

#109. #107 AND #108

#110. #107 NOT #109

#111. #103 NOT #110

#112. #35 AND #89 AND #111

PsycINFO and CINAHL (EBSCOHost platform)

(11/04/2015)

S1 (MH "Herpes Genitalis") 1,074

S2 TX Herpes Genital* 1,512

S3 TX herpesvirus 1,569

S5 (S1 OR S2 OR S3 OR S4) 8,923

S4 TX herpes 7,925

S6 Antiviral agent 127

S7 antiviral 16,089

S8 (MH "Antiviral Agents+") OR (MH "Antiretroviral Therapy, Highly Active") OR (MH "Acyclovir") 27,872

S9 TX imiquimod 249

S10 TX interferron 1

S11 TX interferon 8,169

S12 TX famciclovir 163

S13 TX valaciclovir 49

S14 TX ac?clovir 1,385

S15 TX anti viral 283

S16 TX virucid 0

S17 TX virucide 5

S18 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S1736,571

S19 S5 AND S18 1,981

S20 TX first time 32,862

S21 TX initial 150,983

S22 TX first episode* 8,304

S23 TX first occurrence* 879

S24 TX primary episode* 390

S25 TX primary occurrence* 405

S26 TX index 300,549

S27 TX primary presentation 740

S28 S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 479,355

S29 S19 AND S28 125

LILACS (iAHx interface)

(02/04/2016)

(mh:(herpes genital)) OR (ti:(herpes)) OR (ab:(herpes)) AND db:("LILACS") AND type_of_study:("clinical_trials")

RCTs filter:

((PT:"ensayo clinico controlado aleatorio" OR PT:"ensayo clinico controlado" OR PT:"estudio multicéntrico" OR MH:"ensayos clinicos controlados aleatorios como asunto" OR MH:"ensayos clinicos controlados como asunto" OR MH:"estudios multicéntricos como asunto" OR MH:"distribución aleatoria" OR MH:"método doble ciego" OR MH:"metodo simple-ciego") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble $ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH:animales OR MH:conejos OR MH:ratones OR MH:ratas OR MH:primates OR MH:perros OR MH:gatos OR MH:porcinos OR PT:"in vitro")

Specialised Register of the Cochrane Sexually Transmitted Infections Review Group

(11/04/2016)

1 (herpes:AB) AND (INREGISTER) 57

2 (herpes:TI) AND (INREGISTER) 127

#3 #1 OR #2 132

AMED (Allied and Complementary Medicine)

(02/04/2016)

1 exp Herpes Genitalis/ (8)

2 herpes.tw. (327)

3 exp Herpes Simplex/ (86)

4 simplexviru$.tw. (0)

5 simplex viru$.tw. (110)

6 marmoset virus$.tw. (0)

7 or/2-6 (327)

8 genital$.tw. (672)

9 venereal.tw. (12)

10 anogenital.tw. (2)

11 rectal.tw. (265)

12 anal.tw. (99)

13 anorectal.tw. (22)

14 perianal.tw. (8)

15 penile.tw. (80)

16 penis.tw. (39)

17 vaginal.tw. (200)

18 vulva$.tw. (20)

19 vulvovaginal.tw. (8)

20 or/8-19 (1276)

21 7 and 20 (23)

22 hsv 2.tw. (31)

23 hsv2.tw. (0)

24 or/1,21-23 (52)

25 antivir$.tw. (589)

26 ac?clovir.tw. (27)

27 valac?clovir.tw. (7)

28 famciclovir.tw. (2)

29 exp Interferons/ (32)

30 interferon$.tw. (255)

31 imiquimod.tw. (1)

32 exp Plants medicinal/ (19460)

33 exp Plant extracts/ (22462)

34 (biological adj5 agent$).tw. (65)

35 (biologic$ adj5 product$).tw. (818)

36 (natural adj5 product$).tw. (911)

37 exp Antiviral agents/ (521)

38 Plant extract$.tw. (15650)

39 or/25-38 (27988)

40 24 and 39 (33)

Alternative Medicines Specialised Register

(26/06/2015)

herpe*

Appendix 2. Data extraction form

Data collection form

Notes on using a data extraction form:

- Be consistent in the order and style you use to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.

Review title or ID
Interventions for men and women with their first episode of genital herpes RH124

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

Notes:

1. General Information

Date form completed *(dd/mm/yyyy)*
Name/ID of person extracting data
Report title

(Continued)

(title of paper/ abstract/ report that data are extracted from)

Report ID

(ID for this paper/ abstract/ report)

Reference details

Report author contact details

Publication type

(e.g. full report, abstract, letter)

Study funding sources

(including role of funders)

Possible conflicts of interest

(for study authors)

Notes:

2. Study Eligibility

Study Characteristics	Eligibility criteria *(Insert eligibility criteria for each characteristic as defined in the Protocol)*	Yes	No	Unclear	Location in text *(pg & ¶/fig/ table)*
Type of study	Published and unpublished randomised controlled trials will be included with the exception of those that are quasi-randomised Inclusions: - Drug dosing trials - Suppressive therapy regimes (long-term therapy) for first episodes Exclusions: - Studies of vaccinations. - Studies of complications of HSV				
Participants	Men and women with their first episode of genital herpes				

(Continued)

	Inclusions: - Immunodeficient individuals Exclusions: - Animal models
Types of intervention	• Antivirals (e.g. acyclovir, valaciclovir) - both topical and systemic • Interferon - both topical and systemic • Imiquimod - topical or analogue • Natural products All to be compared with no treatment or placebo or other medication
Types of outcome measures	Primary outcomes 1. Duration of symptoms from onset of treatment (e.g. pain, itching) 2. Duration of lesions from onset of treatment 3. Time to first recurrence Secondary outcomes 4. Adverse events 5. Neonatal effects 6. Caesarean section delivery 7. Viral shedding

INCLUDE	**EXCLUDE**
Reason for exclusion	

Notes:

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description	**Location in text**
	Include comparative information for each group (i.e. intervention and controls) if available	*(pg & ¶/fig/table)*

(Continued)

Population description *(from which study participants are drawn)*	
Setting *(including location and social context)*	
Inclusion criteria	
Exclusion criteria	
Method/s of recruitment of participants	
What day after onset of symptoms was intervention given	Is the day of treatment reported? Yes No Unclear If reported, is it ≤ 5 or > 5 days? ≤ 5 > 5 days (more than 5)
Informed consent obtained	Yes No Unclear
Notes:	

4. Methods

	Descriptions as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Aim of study		

(Continued)

Design *(e.g. parallel, cross-over, cluster)*

Unit of allocation

(by individuals, cluster/ groups or body parts)

Start date

End date

Total study duration

Ethical approval needed/obtained for study

Yes No Unclear

Notes:

5. 'Risk of bias' assessment

See Chapter 8 of the Cochrane Handbook

Domain	Risk of bias			Support for judgement	Location in text
	Low risk	High risk	Unclear		*(pg & ¶/fig/table)*
Random sequence generation: **Was the allocation sequence adequately generated?** *(selection bias)*					
Allocation concealment: **Was allocation adequately concealed?** *(selection bias)*					
Blinding of participants:					

(Continued)

Was knowledge of the allocated intervention adequately prevented during the study? *(performance bias)*
Blinding of personnel *(performance bias)*
Blinding of outcome assessment *(detection bias)*
Incomplete outcome data: **Were incomplete outcome data adequately addressed?** *(attrition bias)*
Selective outcome reporting: **Are reports of the study free of suggestion of selective outcome reporting?** *(reporting bias)*
Notes:

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomised		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances: ***Were the intervention and control groups comparable at baseline?***		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		

(Continued)

Sex	
Race/ethnicity	
Co-morbidities	
Other treatment received *(additional to study intervention)*	
Other relevant sociodemographics	

(Continued)

Subgroups measured			
Subgroups reported			
Have they detailed by antibodies the type of first episodes?	Primary only	Both primary and non-primary	Not stated
If both primary and non-primary, have they analysed separately?	Yes	No	
Notes:			

7. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1 -

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomised to group (specify whether no. people or clusters)		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers (e.g. no., profession, training, ethnicity etc. if relevant)		
Co-interventions		
Notes:		

Intervention Group 2 -

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		

(Continued)

No. randomised to group *(specify whether no. people or clusters)*
Description *(include sufficient detail for replication, e.g. content, dose, components)*
Duration of treatment period
Timing *(e.g. frequency, duration of each episode)*
Delivery *(e.g. mechanism, medium, intensity, fidelity)*
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*
Co-interventions
Notes:

Intervention Group 3 -

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		

(Continued)

Co-interventions

Notes:

Intervention Group 4 -

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Notes:		

8. Outcomes & results

Outcome: Duration of symptoms from onset of treatment

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Notes:		

Results: Continuous outcome - duration of symptoms from onset of treatment

	Description as stated in report/paper						Location in text
							(pg & ¶/fig/table)
Results	**(Insert name of group)**			**(Insert name of group)**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
	(Insert name of group)			**(Insert name of group)**			
	Mean	SD (or other variance)	No. Participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							

(Continued)

Any other results reported	
Unit of analysis *(individuals, cluster/groups or body parts)*	
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Outcome: Duration of lesions from onset of treatment

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Notes:		

Results: Continuous outcome - duration of lesions from onset of treatment

	Description as stated in report/paper						Location in text (pg & ¶/fig/table)
Results	**(Insert name of group)**			**(Insert name of group)**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
	(Insert name of group)			**(Insert name of group)**			
	Mean	SD (or other variance)	No. Participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							

(Continued)

Any other results reported	
Unit of analysis *(individuals, cluster/groups or body parts)*	
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Outcome: Time to first recurrence

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Notes:		

Results: Continuous outcome – time to first recurrence

	Description as stated in report/paper						Location in text (pg & ¶/fig/table)
Timepoint *(specify whether from start or end of intervention)*							
Results	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
	Comparison 2			**Comparison 3**			
	Mean	SD (or other variance)	No. Participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							

(Continued)

No. participants moved from other group and reasons	
Any other results reported	
Unit of analysis *(individuals, cluster/groups or body parts)*	
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Outcome: Caesarean section delivery

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Notes:		

Results: Dichotomous outcome - caesarean section delivery

	Description as stated in report/paper				Location in text (pg & ¶/fig/table)
Results	**(Insert name of group)**		**(Insert name of group)**		
	No. events	No. participants	No. events	No. participants	
	(Insert name of group)		**(Insert name of group)**		
	No. Events	No. Participants	No. Events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis *(by individuals, cluster/groups or body parts)*					

(Continued)

Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Outcome: Neonatal effects

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Notes:		

Results: Dichotomous outcome - neonatal effects

	Description as stated in report/paper				Location in text (pg & ¶/fig/table)
Results	**(Insert name of group)**		**(Insert name of group)**		
	No. events	No. participants	No. events	No. participants	
	(Insert name of group)		**(Insert name of group)**		
	No. Events	No. Participants	No. Events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					

(Continued)

Unit of analysis *(by individuals, cluster/groups or body parts)*	
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Outcome: Adverse events

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Notes:		

Results: Dichotomous outcome - adverse events

	Description as stated in report/paper				Location in text (pg & ¶/fig/table)
Results	**(Insert name of group)**		**(Insert name of group)**		
	No. events	No. participants	No. events	No. participants	
	(Insert name of group)		**(Insert name of group)**		
	No. Events	No. Participants	No. Events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify)*					
	Yes No Unclear				
Reanalysis possible?					

(Continued)

	Yes	No	Unclear
Reanalysed results			
Notes:			

9. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

(Continued)

HISTORY

Protocol first published: Issue 7, 2013
Review first published: Issue 8, 2016

Date	Event	Description
13 March 2009	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Rachel Heslop - Took the lead in writing the protocol, co-ordinating and performing the original search and subsequent searches, performed independent data extraction and quality assessment of the included trials, entered study details and data into Review Manager 5 (RevMan 2014), primarily constructed additional tables and figures, took the lead in writing the description of studies and 'Characteristics of included studies' tables, contributed to 'Effects of interventions' and provided comments on the 'Discussion' and 'Authors' conclusions'.

Helen Roberts - Wrote the first draft of the 'Background', 'Discussion' and 'Authors' conclusions'. Helped with editing of the final draft.

Deralie Flower - Helped with assessing trials for inclusion, as well as data extraction of the included studies. Deralie read and commented on the text of this review.

Vanessa Jordan - Participated in screening of studies and extracting data, either as a second party or as a third party reviewer. Vanessa also created the 'Summary of findings' tables and wrote and edited some of the text of this review. Vanessa took the lead in the co-ordination of the conclusion of this project.

DECLARATIONS OF INTEREST

Rachel Heslop: None known.
Helen Roberts: None known.
Deralie Flower: None known.
Vanessa Jordan: None known.

SOURCES OF SUPPORT

Internal sources

- University of Auckland, New Zealand.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

'Severity' was removed from the objectives in consultation with clinical experts, as this was determined to be not as clinically relevant and would not be reported by the primary studies as it is too difficult to measure.

In this review we have added the words "inclusive of pregnant women" to the participant inclusion criteria. This resulted from a suggestion made during the editorial process of this review in which we were asked to clarify this aspect of the inclusion criteria.

In the protocol we initially planned to subgroup by mode of delivery and dose however with further clinical input with regard to the structure of this review we subsequently decided to analyse the different modes of delivery separately and it was concluded that dose would not be substantially different in any of the studies. In addition a new subgroup was introduced, 'first episode of primary infection versus first episode of non-primary infection.' As symptomatic first episode of primary infection herpes is usually more severe than a first episode of non primary infection in an already infected individual, it is important to ascertain that interventions are effective for these individuals experiencing a true first episode of primary infection. Please refer to Background.

The summary of findings table outcomes were not prespecified in the original protocol for this review and so these have been chosen based on perceived clinical interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Acyclovir [adverse effects] [analogs & derivatives] [therapeutic use]; Administration, Oral; Antiviral Agents [adverse effects] [therapeutic use]; Herpes Genitalis [*drug therapy]; Injections, Intravenous; Randomized Controlled Trials as Topic; Recurrence; Valacyclovir; Valine [adverse effects] [analogs & derivatives] [therapeutic use]

MeSH check words

Female; Humans; Male