Topical microbicides for prevention of sexually transmitted infections (Review)

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TABLE OF CONTENTS

[Intervention Review]

Topical microbicides for prevention of sexually transmitted infections

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ABSTRACT

Background

Two decades of research on topical microbicides for prevention of sexually transmitted infections (STIs) have had limited success. However, new microbicide randomised controlled trial (RCT) data have recently been published; but these have not yet been the subject of a systematic review.

Objectives

To determine the effects of topical microbicides for prevention of the acquisition of STIs, including human immunodeficiency virus (HIV) infection, by women from men and by men who have sex with men (MSM).

Search methods

In July 2011 we searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, Web of Science, NLM Gateway, CLIB, AIDS Education Global Information System, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform; handsearched reference lists of relevant articles and contacted relevant organisations and experts.

Selection criteria

RCTs of topical microbicides (except Nonoxynol-9) in sexually active, HIV-negative women or MSM. We excluded Nonoxynol-9 because previous systematic reviews showed that it does not have a significant effect on HIV or STIs.

Data collection and analysis

We assessed study eligibility, extracted data and assessed risk of bias in duplicate; resolving differences by discussion and consensus. We then conducted fixed-effect meta-analysis, stratified by type of microbicide.

Main results

We found that by the end of 2011, nine microbicide RCTs had either been conducted to term (one BufferGel and 0.5% PRO 2000, one Carraguard and one tenofovir trial) or stopped early due to safety concerns (two cellulose sulphate trials) or insufficient rate of HIV infection and low likelihood of showing a protective effect (one 2% PRO 2000, one tenofovir and two SAVVY trials). The nine

RCTs enrolled 31,941 sexually active women between 2004 and 2011; in Benin, Ghana, Malawi, Nigeria, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, India, and the US. A small proof-of-concept RCT found that tenofovir (a nucleotide reverse transcriptase inhibitor) reduced the risk of HIV acquisition (one trial, 889 women; risk ratio (RR) 0.63; 95% CI 0.43 to 0.93). Effectiveness data are not yet available from the second tenofovir RCT that enrolled 5000 women and was stopped early due to low likelihood of showing a protective effect. We found no evidence of an effect on HIV acquisition for cellulose sulphate (2 trials, n = 3069; RR 1.20; 95% CI 0.74 to 1.95), SAVVY (two trials, n = 4295; RR 1.38; 95% CI 0.79 to 2.41), Carraguard (one trial, n = 6202; RR 0.89; 95% CI 0.71 to 1.11), PRO 2000 (two trials, n = 12,486; RR 0.93, 95% CI 0.77 to 1.14) and BufferGel (one trial, n = 1546; RR 1.05; 95% CI 0.73 to 1.52). Tenofovir reduced the incidence of herpes simplex virus type 2 (HSV-2) infection (one trial, 426 women; RR 0.55; 95% CI 0.37 to 0.83) and cellulose sulphate reduced the risk of chlamydia infection (two trials, n = 3069; RR 0.70, 95% CI 0.49 to 0.99). However, there was no evidence of an effect of any microbicide on the acquisition of gonorrhoea, syphilis, condyloma acuminatum, trichomoniasis, or human papillomavirus (HPV) infection. A substudy of the Carraguard trial found the prevalence of high-risk HPV infection (HR-HPV) to be 23.5% in women on Carraguard and 23.0% on placebo (n = 1718; RR 1.02; 95% CI 0.86 to 1.21). After controlling for HR-HPV risk factors, the authors found that compliant Carraguard users were 0.62 (95% CI 0.41 to 0.94) times as likely to be HR-HPV positive as compliant placebo users. Overall, there was no significant difference in the incidence of adverse events between microbicide and placebo groups.

Authors' conclusions

Limited evidence suggests that vaginal tenofovir microbicides may reduce the risk of acquisition of HIV and HSV-2 infections in women; but other types of topical microbicides have not shown evidence of an effect on HIV or STI acquisition. Therefore, there is not enough evidence to recommend topical microbicides for HIV or STI prevention at present. Further studies are needed to confirm the beneficial effects of tenofovir microbicide gel in vaginal sex. In addition, further research should continue on the development and testing of new microbicides. If the effectiveness of the tenofovir and/or other microbicides is confirmed in further studies, there will need to be a clear pathway to rapid regulatory approval. Successful launch of the effective gel would depend on having in place appropriate mechanisms for distribution to the women who need it, along with a strategy for ensuring that they use it correctly.

PLAIN LANGUAGE SUMMARY

Topical microbicides for prevention of sexually transmitted infections

Microbicide research has had disappointing outcomes during the last two decades as most microbicides have not shown evidence that they can prevent acquisition of sexually transmitted infections (STIs), including human immunodeficiency virus (HIV). However, a recent small preliminary study suggests that microbicides containing the antiretroviral drug tenofovir may prevent acquisition of HIV and herpes simplex virus infection in women; but further research is needed to assess the generalisability of these findings. Therefore, there is not enough evidence to recommend topical microbicides for HIV or STI prevention at present.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Use of topical microbicides compared to placebo for preventing HIV and other sexually transmitted infections

Patient or population: Heterosexual women
Settings: Africa (all 8 studies), USA (1 study)
Intervention: Use of any topical microbicide
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Use of any topical microbicide			
HIV infection	42 per 1000	39 per 1000 (34 to 44)	RR 0.93 (0.82 to 1.05)	24,192 (8 studies)	⊕⊕◯◯ low[1]
Herpes simplex virus	43 per 1000	35 per 1000 (23 to 37)	RR 0.83 (0.67 to 1.02)	8502 (2 studies)	⊕⊕◯◯ low[2,3]
Gonorrhoea	48 per 1000	49 per 1000 (42 to 56)	RR 1.01 (0.88 to 1.16)	15,921 (4 studies)	⊕⊕◯◯ low[3,5]
Chlamydia	69 per 1000	64 per 1000 (57 to 72)	RR 0.93 (0.83 to 1.04)	15,922 (4 studies)	⊕⊕◯◯ low[3,5]
Syphilis	18 per 1000	18 per 1000 (13 to 26)	RR 1.01 (0.73 to 1.41)	7627 (2 studies)	⊕⊕◯◯ low[3,4]
Trichomoniasis	80 per 1000	69 per 1000 (59 to 81)	RR 0.86 (0.74 to 1.01)	7627 (2 studies)	⊕⊕◯◯ low[3,4]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One small trial suggests that tenofovir reduces the risk of HIV acquisition (RR 0.63; 95% CI 0.43 to 0.93), but none of the other types of microbicides show evidence of an effect. Five of eight trials stopped early due to data-dependent processes: rated down by 2.
[2] One small trial suggests that tenofovir reduces the risk of HSV-2 acquisition (RR 0.55; 95% CI 0.37 to 0.83), but none of the other types of microbicides show evidence of an effect: rated down by 1
[3] Wide confidence intervals: rated down by 1
[4] Only 2 trials reported this outcome: rated down by 1
[5] Only 4 trials reported outcome: rated down by 1

BACKGROUND

Description of the condition

Sexually transmitted infections (STIs), including human immunodeficiency virus (HIV) infection, continue to cause disease, disability and death among millions of young women despite the prevention efforts implemented to date (Low 2006; UNAIDS 2010). This unacceptable situation demands the development of safe, effective and acceptable female-controlled methods to reduce transmission.

Description of the intervention

Topical microbicides are chemical agents that can be used vaginally or rectally to kill or disable disease-causing organisms such as viruses, bacteria, fungi or protozoa (D'Cruz 2004; Elias 1994; Fleck 2004; Isaacs 2006). The ideal microbicide would be active against a range of STI-causing organisms, available in both spermicidal and non-spermicidal formulations, effective over relatively long periods, acceptable to potential users, easy to use and affordable, bio-diffusible, bio-adhesive, be effective immediately, be stable at high temperatures, maintain or enhance normal vaginal ecology, and neither be irritating to mucosal surfaces nor be absorbed systemically.

How the intervention might work

Topical microbicides that have been developed include detergents that disrupt viral, bacterial and cell membranes; acid-buffering agents that maintain the natural vaginal acidity; sulphated or sulphonated polysaccharides that bind to viruses or bacteria to prevent them from attaching to and infecting healthy cells and antiretroviral (ARV) agents that prevent the replication of the pathogen after it has entered the cell (Abdool Karim 2010; Harrison 2003; Mahmoud 1995; Stone 1986; Stone 2002; Zetlin 2001).

Why it is important to do this review

Over the last decade more than 60 substances were identified as potential intravaginal or rectal microbicides and about a quarter of these have reached various stages of human testing (Brown 2004; Cutler 2008; Fleck 2004; Ramjee 2000). A number of studies have examined the safety, efficacy and tolerability of topical microbicides in preventing STIs (Harwell 2003; Mayer 2001; van De Wijgert 2001; Zetlin 2001). However, we are not aware of an up-to-date published systematic review of these studies. This review sought to combine the evidence from published and unpublished randomised controlled trials (RCTs) that assessed the effects of topical microbicides on the incidence of STIs and HIV infection, in sexually active women and men who have sex with men (MSM).

OBJECTIVES

To determine the effects of topical microbicides for prevention of acquisition of STIs, including HIV infection, by women from men and MSM.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Sexually active women and MSM in any setting, who had no clinical signs or laboratory-confirmed STIs.

Types of interventions

Topical microbicides compared with no treatment, placebo or barrier methods for STI prevention (such as the condom, diaphragm, vaginal sponge and cervical cap*)*. Nonoxynol-9 was excluded because it is covered in other Cochrane reviews (Wilkinson 2002a; Wilkinson 2002b).

Types of outcome measures

Primary outcomes

- Incidence of STIs - viral, bacterial, fungal or protozoan

Secondary outcomes

- Acceptability
- Safety
- Adverse events

Search methods for identification of studies

See: Cochrane HIV/AIDS Group methods used in reviews.
We searched for all relevant studies regardless of language or publication status (published, unpublished).
We compiled detailed search strategies in consultation with the Trials Search Co-ordinators of the Cochrane HIV/AIDS Group and the Sexually Transmitted Infections Group. This was based on comprehensive search strategies for STIs and HIV, combined with the Cochrane Highly Sensitive Search Strategy for Randomised Controlled Trials as published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The sensitive search strategies consisted of both controlled vocabulary terms and free text terms in combination with intervention terms.

Electronic searches

We searched the following electronic databases in May 2009, December 2009 and July 2011:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (22 July 2011),
- MEDLINE (1980 to 22 July 2011),
- EMBASE (1980 to 22 July 2011),
- Web of Science (1980 to 26 May 2009),
- LILACS (1980 to 14 May 2009),
- NLM Gateway (1980 to 4 December 2009).

Details of the search strings used for the individual databases are outlined in Appendix 1, Appendix 2 and Appendix 3.
We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov in July 2011 for ongoing microbicide trials.
In addition, on 13 January 2012 we searched PubMed to verify if studies previously identified as ongoing had been published.

Searching other resources

We conducted searches of conference proceedings and reference lists of relevant journal articles and contacted organisations involved in microbicide research.

Conference proceedings

We searched proceedings of the following conferences (from 1980 to July 2011) for relevant studies:

- International Conference on AIDS and STDs in Africa (ICASA),
- biennial meeting of the International Society for Sexually Transmitted Diseases Research,
- International Congress of Sexually Transmitted Infections and
- Biannual International Microbicide Conference and Modern Mucosal Vaccines, Adjuvants and Microbicides.

Researchers, organisations and pharmaceutical companies

We contacted organisations involved in microbicide research, including the Alliance for Microbicide Development, International Partnership for Microbicides (IPM), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and WHO. In addition, we also contacted microbicide and HIV prevention experts.

Reference lists

We checked the reference lists of relevant previous reviews (Buckeit 2010; Cutler 2008; Garg 2009; Klasse 2008; Nuttall 2010) and full-text articles reviewed for inclusion in this review (Abdool Karim 2010; Abdool Karim 2011; Artz 2005; Ettiegne-Traore 1997; Feldblum 2008; Halpern 2008; Lourens 2002; McCormack 2010; Peterson 2007; Rosenberg 1987; Skoler-Karpoff 2008; Straten 2007; Van Damme 2008).

Data collection and analysis

Selection of studies

Two review authors (JO and CSW) independently scanned the citations and abstracts identified by the search strategies described above to establish a list of articles that were potentially eligible for inclusion in the review, compared the two lists, and (once consensus was reached) obtained the full-text articles of all potentially eligible studies. The two review authors then independently reviewed the relevance of the full-text articles for inclusion in the review based on study design, types of participants, interventions and outcome measures. Following the eligibility assessment, each study was classified as included, excluded, ongoing or awaiting assessment. A study that met the design, intervention and participant criteria for which relevant outcomes were not yet available was classified as ongoing (if the study was not yet completed) or awaiting assessment (if the study was completed but data had not yet been published and we could not get any relevant outcome data from trial investigators). We have given reasons for excluding potentially relevant trials in the table of Characteristics of excluded studies. Any differences in opinion between the two review authors were resolved by discussion and consensus. The third review author (PGM) would have arbitrated if any disagreement persisted.

Data extraction and management

The two review authors independently extracted data from included studies using a pre-designed and pilot-tested data extraction form. Extracted information included:

- study details: citation, study design, population size and attrition rate,
- participant details: study population demographics and risk characteristics,

- intervention details: type of intervention, time period for the intervention and length of follow-up,
- outcome details: primary and secondary outcomes and their definitions, including types of laboratory tests used to confirm STI or HIV diagnosis,
- study results: total number of participants in each study arm and number of participants with each outcome,
- additional notes: correspondence with study authors, clarification of queries, language of publication of the study, relevant studies identified in the reference list.

Differences in opinion between the two review authors on data extraction were resolved by discussion and consensus. The third review author arbitrated if any disagreement persisted.

Assessment of risk of bias in included studies

Two review authors (JO, CSW) independently assessed the risk of bias within each included study by addressing seven specific domains, namely, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. For each included study, the two review authors independently described what the study authors reported that they did for each domain and then made a decision relating to the risk of bias for that domain by assigning a judgement of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias. The review authors compared the results of their independent assessments of risk of bias and resolved any discrepancies by discussion and consensus. The third review author arbitrated if any discrepancy persisted.

Measures of treatment effect

We expressed study results as risk ratios (RR) with 95% confidence intervals (CI).

Assessment of heterogeneity

We assessed heterogeneity between trial results using the Chi^2 test of homogeneity, with statistical significance defined at the 10% alpha level. In addition, we used the I^2 test to quantify the degree of heterogeneity as follows: low (I^2 value below 40%), moderate (I^2 value of 40% to 75%) or high (I^2 value above 75%).

Data synthesis

We analysed all participants in the groups to which they were randomised, irrespective of which or how much treatment they received. There was no significant statistical heterogeneity between trial results for any outcome, so we combined the results using fixed-effect meta-analyses. We stratified the analyses by type of microbicide.

Subgroup analysis and investigation of heterogeneity

We subgrouped the trials by type of microbicide for all outcomes. We planned to explore the possible causes of any significant statistical heterogeneity by using subgroup analyses; with subgroups defined by the sex of study participants, type of sexual orientation (heterosexual or homosexual) and type of (active) comparison group (condom, diaphragm, vaginal sponge or cervical cap).

Sensitivity analysis

We conducted sensitivity analyses to investigate the effect of type of meta-analysis (fixed-effect or random-effects) on the robustness of the results. Given that there was no significant statistical heterogeneity, the method of meta-analysis did not have a significant impact on the results.

RESULTS

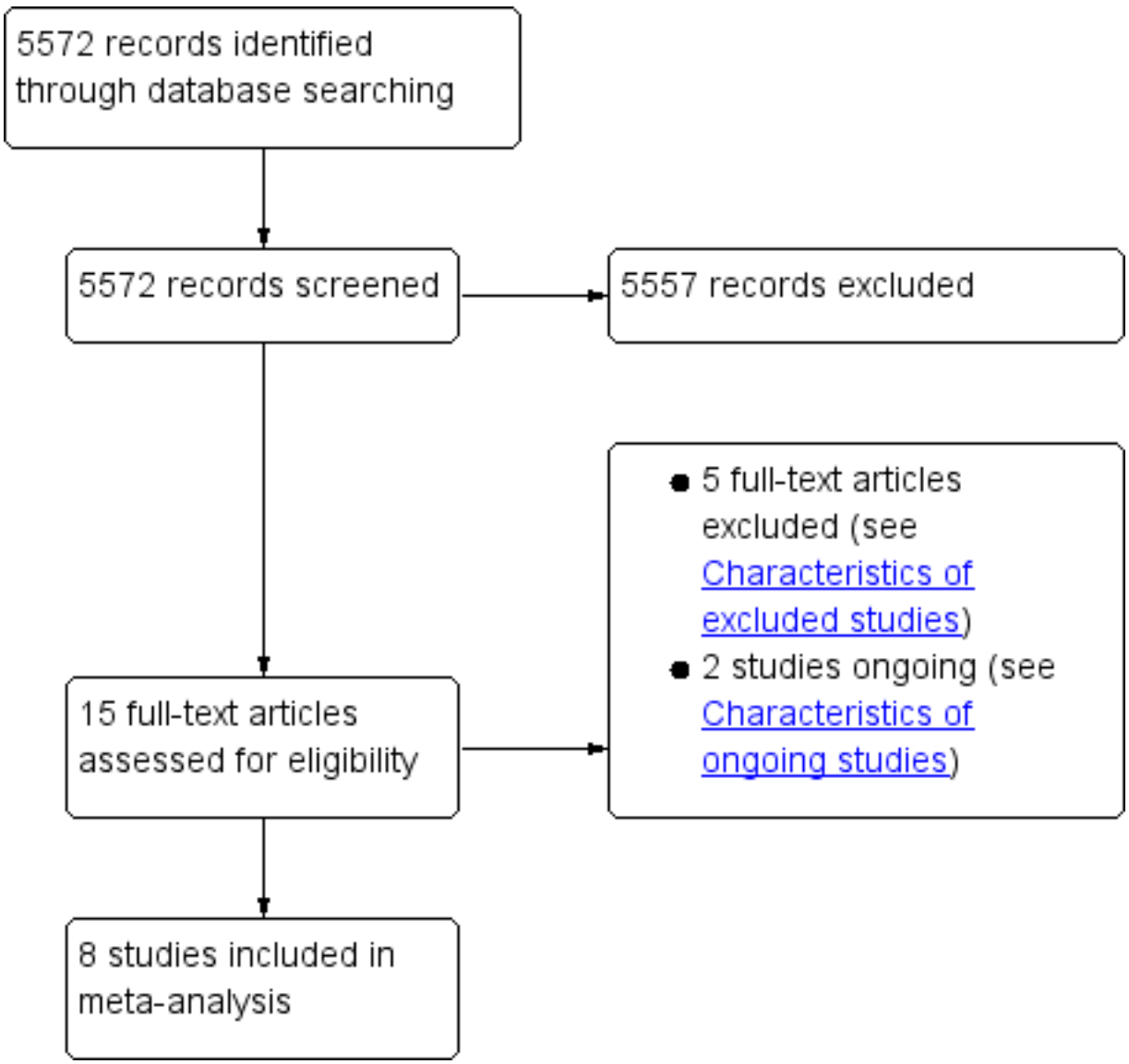
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See: Characteristics of included studies.

Results of the search

A total of 3239 articles were retrieved from the search conducted in May 2009 by the Sexually Transmitted Infections Review Group (Table 1), and 1942 (Table 2) and 391 articles (Table 3) were retrieved from the search conducted in December 2009 and July 2011, respectively, by the HIV/AIDS Review Group. Following independent duplicate screening of both search outputs, we retrieved the full-text of 15 potentially eligible articles and reviewed them for inclusion. Of these, we included eight (Abdool Karim 2010; Abdool Karim 2011; Feldblum 2008; Halpern 2008; McCormack 2010; Peterson 2007; Skoler-Karpoff 2008; Van Damme 2008), excluded five (Artz 2005; Ettiegne-Traore 1997; Lourens 2002; Rosenberg 1987; Straten 2007), and two (NCT00705679; NCT01386294) were ongoing in July 2011. The search in January 2012 identified one potentially eligible study (Marais 2011), but this is a substudy of an already included trial (Skoler-Karpoff 2008). In addition, we identified a press release (AVAC 2011) announcing that one of the studies we previously identified as ongoing (NCT00705679) would stop early.
The process of searching and selection of studies for this review is presented in the PRISMA flow diagram in Figure 1.

Figure 1. PRISMA study flow diagram showing the search and selection of studies for this review.



Included studies

See: Characteristics of included studies.

All eight included studies enrolled sexually active women and had HIV incidence as the primary outcome (Abdool Karim 2010; Abdool Karim 2011; Feldblum 2008; Halpern 2008; McCormack 2010; Peterson 2007; Skoler-Karpoff 2008; Van Damme 2008). We did not find an eligible study that enrolled MSM. At the commencement of each of the eight trials, all participating women were screened for pregnancy, HIV, other STIs and reproductive tract infections. All the 26,941 women recruited by the eight studies were HIV-negative at the start of the studies. Participants were counselled and supplied with free condoms, which they were instructed to use for all acts of sexual intercourse regardless of gel use. Women were instructed to insert contents of the applicator of their assigned study gel into the vagina within the hour preceding each act of vaginal intercourse. The age of trial participants ranged from 16 to 72 years. Women randomised to the intervention arm were offered topical microbicide gels and those on the control arm were offered placebo gels. Six different microbicide

gels were used, namely, cellulose sulphate (CS) (Halpern 2008; Van Damme 2008), SAVVY (Feldblum 2008; Peterson 2007), PRO 2000 (Abdool Karim 2011; McCormack 2010), BufferGel (Abdool Karim 2011), Carraguard (Skoler-Karpoff 2008) and tenofovir (Abdool Karim 2010).

The Halpern 2008 CS trial (n = 1644) was conducted in Lagos and Port Harcourt, Nigeria. The trial commenced in 2004 and follow-up was planned for 12 months. The Van Damme 2008 CS trial (n = 1428) was conducted in Benin, India, and South Africa. The trial commenced in 2005 and follow-up was planned for 12 months. The pH of the CS used in both trials was 7.5. The Van Damme 2008 trial was stopped prematurely in January 2007 after the Data Safety Monitoring Board (DSMB) determined that the CS gel may have increased the risk of HIV infection when compared with placebo. This decision also led to the early discontinuation (in the same month) of the parallel CS trial being conducted in Nigeria (Halpern 2008). The last follow-up visit for each RCT occurred in March 2007.

The Peterson 2007 SAVVY trial (n = 2142) was conducted in Accra and Kumasi, Ghana, and the Feldblum 2008 SAVVY trial (n = 2153) was conducted in Lagos and Ibadan, Nigeria. The pH of the SAVVY gel used in the trials was 4.4. Both trials commenced in 2004 and follow-up was planned for 12 months. Following the recommendation of the respective DSMB, each study was stopped prematurely (Peterson 2007 in November 2005 and Feldblum 2008 in August 2006) because the HIV incidence among enrolled participants was too low to offer the desired power to detect an effect of the microbicide on HIV acquisition.

The McCormack 2010 PRO 2000 trial (n = 9385) was conducted in South Africa, Tanzania, Uganda and Zambia. The trial commenced in September 2005 and follow-up was planned for 24 months. The 2% PRO 2000 gel was discontinued early (14 February 2008) after a review by the DSMB. The DSMB advised that there was little chance of the 2% PRO 2000 gel showing benefit given the planned sample size and postulated effect size. However, the conditional power for significant benefit from the 0.5% PRO 2000 dose (based on the original sample size assumptions) was sufficiently high to warrant trial continuation. The Abdool Karim 2011 BufferGel and 0.5% PRO 2000 trial (n = 3101) was conducted in Malawi, South Africa, Zambia, Zimbabwe and the US. The trial commenced in 2005 and followed up study participants for an average of 20.4 months.

The Skoler-Karpoff 2008 Carraguard trial (n = 6202), which commenced in 2004, was conducted in South Africa, and participants were followed up for up to 24 months. A substudy of this trial (Marais 2011; n = 1723) was initiated in October 2006, six months before the study end, to assess the association of HR-HPV with Carraguard use.

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 tenofovir proof-of-concept trial (Abdool Karim 2010: n = 889), which commenced in 2007, was conducted in South Africa. Participants were followed up for a total of 1341 women-years (mean = 18 months). Another tenofovir trial, the Vaginal and Oral Intervention to Control the Epidemic (VOICE) trial (NCT00705679), enrolled more than 5000 women in South Africa, Uganda and Zimbabwe. A press release in November 2011 (AVAC 2011) announced that the DSMB recommended that the 1% tenofovir gel arm of the study be stopped and that the women in that arm exit the trial in a structured process. Although the DSMB found no safety issues with the trial, the board concluded that there was no possibility that daily use of tenofovir gel would show efficacy in preventing HIV in the context of the VOICE trial. We classify this trial as ongoing because as of 31 January 2012, no effectiveness data from the trial had been released.

Excluded studies

See: Characteristics of excluded studies.

Five studies were excluded. In three studies (Artz 2005; Ettiegne-Traore 1997; Rosenberg 1987), the microbicide used was Nonoxynol-9, which has already been covered in other Cochrane reviews (Wilkinson 2002a; Wilkinson 2002b). One trial involved in vitro and animal studies (Lourens 2002), while the other (Straten 2007) included HIV- positive participants.

Risk of bias in included studies

We judged the risk of bias related to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective outcome reporting and 'other potential sources of bias' to be low for each of the included studies. Five trials (Feldblum 2008; Halpern 2008; McCormack 2010; Peterson 2007; Van Damme 2008) were stopped early due to data-dependent processes. Due to the early discontinuation, three of the studies had a very high attrition rate: 10% in Van Damme 2008, 16% in Peterson 2007 and 30% in Halpern 2008. We have rated the risk of bias due to incomplete outcome data for each of these studies as high. The remaining studies had losses to follow-up ranging from 3% to 7% (Abdool Karim 2010; Abdool Karim 2011; Feldblum 2008; McCormack 2010; Skoler-Karpoff 2008).

Our judgements about the risk of bias in each included study are summarised in Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

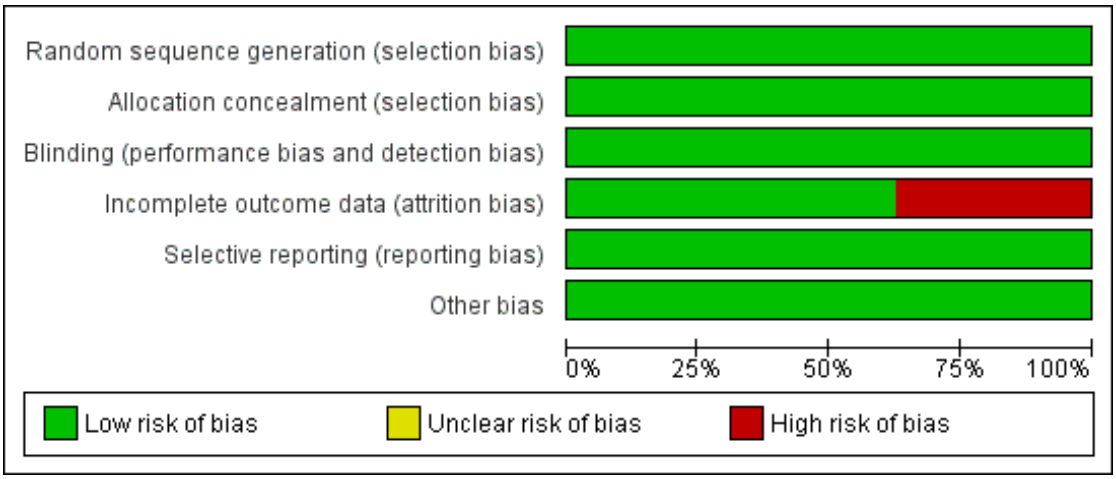
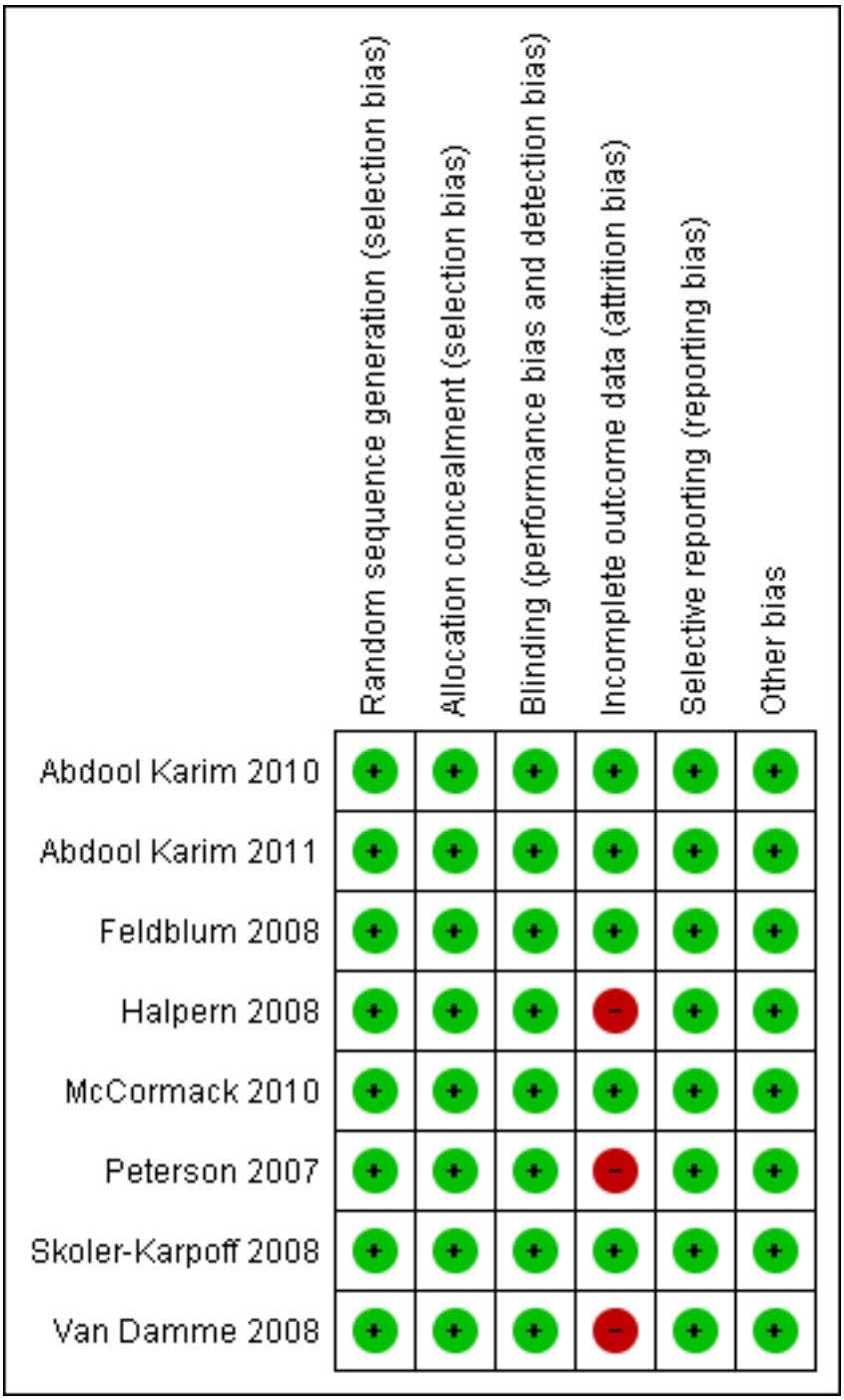


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

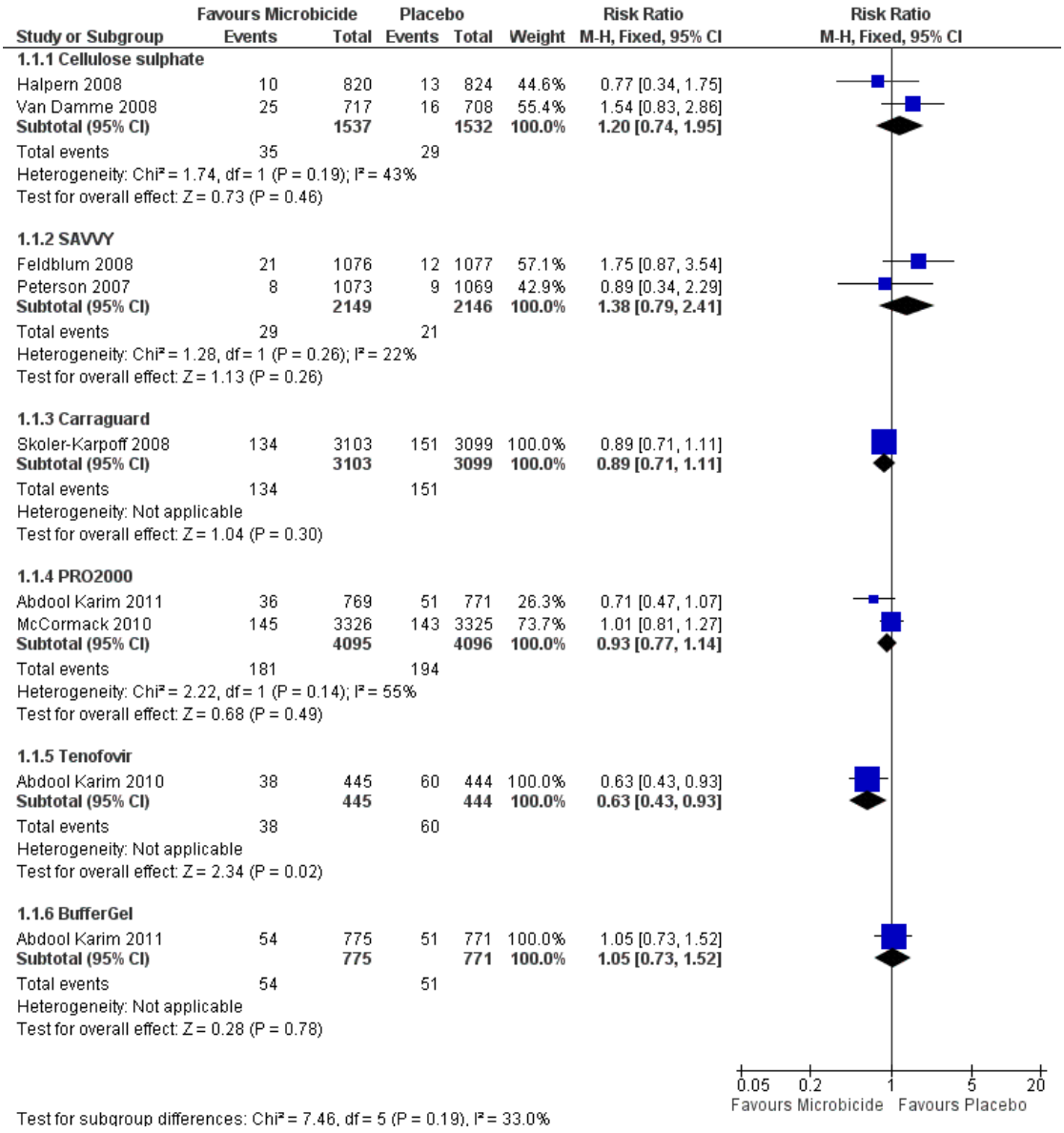
See: **Summary of findings for the main comparison** Use of topical microbicides compared to placebo for preventing HIV and STIs; **Summary of findings 2** Use of tenofovir vaginal microbicide compared to placebo for preventing HIV

Primary outcomes

HIV infection

Different types of microbicides have different modes of action. Thus, we did not pool together data for the six different types of microbicides (Analysis 1.1). In a small proof-of-concept trial of 889 women, vaginal application of a gel made of tenofovir (a nucleotide reverse transcriptase inhibitor) resulted in a significant 37% relative reduction in the risk of HIV acquisition (RR 0.63; 95% CI 0.43 to 0.93 (Abdool Karim 2010)). However, there was no evidence of an effect on the incidence of HIV infection for CS (two trials, 3069 participants; RR 1.20; 95% CI 0.74 to 1.95; I^2 = 43% (Halpern 2008; Van Damme 2008)), SAVVY (two trials, 4295 participants; RR 1.38; 95% CI 0.79 to 2.41; I^2 = 22% (Feldblum 2008; Peterson 2007)), Carraguard (one trial, 6202 participants; RR 0.89; 95% CI 0.71 to 1.11 (Skoler-Karpoff 2008)), 0.5% PRO 2000 (two trials, 9752 participants; RR 0.93; 95% CI 0.77 to 1.14 (Abdool Karim 2011; McCormack 2010)) and BufferGel (one trial, 1546 participants; RR 1.05; 95% CI 0.73 to 1.52 (Feldblum 2008)) (Figure 4).

Figure 4. Forest plot of comparison: 1 Topical microbicide versus placebo - dichotomous data, outcome: 1.1 HIV incidence.



Herpes simplex virus (HSV)

Three studies reported data on HSV acquisition (Abdool Karim 2010; McCormack 2010; Van Damme 2008). Neither CS (Van Damme 2008; n = 1425; RR 0.99; 95% CI 0.37 to 2.62) nor 0.5% PRO 2000 (McCormack 2010; n = 6651; RR 0.95; 95% CI 0.73 to 1.23) had a significant effect on acquisition of HSV infection (Analysis 1.2). However, vaginal application of tenofovir halved the risk of HSV-2 acquisition in a subset of 426 women who were HSV-2 negative at the start of the CAPRISA 004 tenofovir trial (Abdool Karim 2010; RR 0.55; 95% CI 0.37 to 0.83).

Gonorrhoea

Four studies reported data on gonorrhoea (Halpern 2008; McCormack 2010; Skoler-Karpoff 2008; Van Damme 2008). The trials did not find evidence that the effect of vaginal application of CS (two trials, 3069 women; RR 0.89; 95% CI 0.67 to 1.17; I^2 = 50%), Carraguard (one trial, 6202 women; RR 1.06; 95% CI 0.88 to 1.27) or PRO 2000 (one trial, 6651 women; RR 1.04; 95% CI 0.76 to 1.43) microbicide gels was different from that of placebo (Analysis 1.3).

Chlamydia

Chlamydia trachomatis infection was reported by four studies: CS (Halpern 2008; Van Damme 2008), Carraguard (Skoler-Karpoff 2008) and PRO 2000 (McCormack 2010). The combined results suggest that CS may reduce the risk of acquiring chlamydia infection (two trials, 3069 women; RR 0.70; 95% CI 0.49 to 0.99; I^2 = 0%). Neither Carraguard (one trial, 6202 women; RR 0.96; 95% CI 0.83 to 1.12) nor PRO 2000 (one trial, 6651 women; RR 0.97; 95% CI 0.78 to 1.20) had a significant effect on the risk of acquisition of chlamydial infection (Analysis 1.4).

Syphilis

Two trials reported data on the acquisition of syphilis. Their results show that neither CS (Van Damme 2008; one trial, 1425 women; RR 0.69; 95% CI 0.26 to 1.81) nor Carraguard (Skoler-Karpoff 2008; 1 trial, 6202 women; RR 1.07; 95% CI 0.75 to 1.52) has a significant effect on acquisition of syphilis (Analysis 1.5).

Condyloma acuminatum

Condyloma acuminatum was reported by one of the CS studies (Van Damme 2008). This trial showed no evidence that the vaginal microbicide has an effect on acquisition of condyloma acuminatum (1425 women; RR 3.46; 95% CI 0.72 to 16.58; Analysis 1.6).

Trichomoniasis

Trichomoniasis was reported by one CS trial (Van Damme 2008; RR 0.96; 95% CI 0.62 to 1.49) and the Carraguard trial (Skoler-Karpoff 2008; RR 0.85; 95% CI 0.72 to 1.01); none of which showed evidence of an effect of vaginal microbicides on acquisition of trichomoniasis (Analysis 1.7).

Human papillomavirus (HPV)

HPV was reported by a substudy of the Carraguard trial (Skoler-Karpoff 2008). At the end of the study the prevalence of HR-HPV infection was 23.5% in women on Carraguard and 23.0% in the placebo arm (n = 1718; RR 1.02; 95% CI 0.86 to 1.21; Analysis 1.8). The authors found significant risk factors for HR-HPV infection were younger age, being single, an abnormal Pap smear, multiple sex partners and promiscuous behaviour without the use of a condom. After controlling for these risk factors in Poisson regression analysis, the authors found that compliant Carraguard users were 0.62 (95% CI 0.41 to 0.94) as likely to be HR-HPV positive as compliant placebo users (Marais 2011).

Secondary outcomes

Adverse events

Each trial recorded adverse events, including events considered related and not related to the microbicide. The adverse events related to the reproductive tract for the individual studies are listed in separate tables: Table 4 for Feldblum 2008, Table 5 for Halpern 2008, Table 6 for Peterson 2007, Table 7 for Skoler-Karpoff 2008, Table 8 for Van Damme 2008, Table 9 for McCormack 2010, Table 10 for Abdool Karim 2010, Table 11 and Table 12 for Abdool Karim 2011. Candidiasis and vaginal discharge were reported by all studies except the McCormack 2010 PRO 2000 study. The other common adverse events reported by most studies included bacterial vaginosis, pruritus, menorrhagia, ulceration, menstrual disorder, vaginal haemorrhage, laceration and erythema.

In Feldblum 2008, the most frequently self-reported reproductive tract adverse events were vaginal candidiasis, bacterial vaginosis and vulvovaginitis. A subgroup of reproductive tract adverse events included vaginal irritation, vaginal burning and self-reported vaginitis. Twenty-eight severe adverse events occurred during the study (n = 13 in SAVVY and n = 15 in placebo groups). None was deemed to be related to the study product. Two participants discontinued the study as a result of a severe adverse event; one person was hospitalised for appendicitis and the other for typhoid enteritis. Three participants died (n = 1 SAVVY and n = 2 in placebo groups), but the information was limited. The

most frequently reported non-reproductive tract adverse events were malaria, abdominal pain and headache.

In Halpern 2008, a total of 48 severe adverse events were identified, but none was related to the gel use. The most common reproductive tract adverse events were bacterial vaginosis, genital pruritus and candidiasis. Hospitalisation due to malaria and typhoid were the most frequent severe adverse events. Most adverse events were mild and resolved with no sequelae. Adverse event rates were generally the same among study groups.

In Peterson 2007, participants in both groups had adverse events with no significant differences in their overall frequency between treatment groups. The most frequently reported adverse events included malaria, abdominal pain, headache, general pain, genital pruritus, vaginal discharge and vulvovaginitis. Twenty-two severe adverse events were reported (15 in SAVVY and seven in placebo group). Two deaths occurred. One was suspected to be due to possible sickle cell crisis (SAVVY group) and the other was due to viral hepatitis complicated by hepatic encephalopathy (placebo group).

In Skoler-Karpoff 2008, adverse events (most of which were mild or moderate) occurred in 23% of women (both groups). Only 2% of participants had adverse events that were (possibly or probably) related to study gel, the most common of which were genital pruritus (n = 9 Carraguard, n = 10 placebo) and vaginal discharge (n = 9 Carraguard, n = 10 placebo). Overall, severe adverse events occurred in 2% of participants (2% Carraguard, 3% placebo). There were 29 deaths recorded (n = 14 Carraguard, n = 15 placebo). Twenty-six women were advised to suspend their gel use temporarily on the basis of clinical observation (n = 14 Carraguard, n = 12 placebo) because of abnormal epithelial findings or genital adverse events. A participant on placebo who had pre-existing allergy to gels and creams suffered from genital pruritus, and this led to permanent withdrawal of the study gel. The proportion of women with abnormal genital findings or abnormal Pap smears was similar in two groups.

In Van Damme 2008, 86% of women had one or more adverse events during follow-up, with no clinically important differences between the two groups. The most common adverse events were infections and infestations including respiratory tract infections (20.2%), malaria (14.1%) and genital infections (11.4%). Common non-infectious reproductive tract system events included pruritus (8.4%), metrorrhagia (6%) and vaginal discharges (5.1%). There were 68 severe adverse events, none considered related to product use, with more events in the placebo group than in the CS group (n = 40 placebo, n = 28 CS). The most common severe adverse events were abortion or abortion-related events (n = 15) and pyrexia (n = 11). There were three deaths, all in the CS group; one suicide, one murder and one death due to complications of uncontrolled hypertension.

In McCormack 2010, nine deaths occurred in the intervention group and five in the placebo group. No severe adverse events were regarded to be related to study gels. The most common adverse events included non-menstrual bleeding, erythema (internal) and pruritus. Five hundred and ninety-five participants with routine laboratory data experienced at least one systemic toxic event, of which the most common was either high concentrations of aspartate aminotransferase (AST) or bilirubin.

In Abdool Karim 2010, there were 4692 adverse events reported with 94.3% of the study participants reporting at least one adverse event. One death was reported in the placebo group. Three severe adverse events were reported in each group. Other adverse events included influenza, headache, diarrhoea and gastrointestinal infections. Laboratory parameters reported included raised levels of AST or alanine aminotransferase (ALT), raised creatinine, low potassium, raised sodium, anaemia, neutropenia, low phosphate and low calcium. There was no significant difference between intervention and control groups in the frequency of abnormal laboratory test results.

In Abdool Karim 2011, the most common adverse events reported included vaginal discharge, vulvovaginal pruritus, genital infection, genital irritation and urinary tract events. Two deaths were reported in each of the two intervention gel groups and the placebo gel group. However, the differences between each intervention and control groups were not significant.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Use of tenofovir vaginal microbicide compared to placebo for preventing HIV infection

Patient or population: Heterosexual women
Settings: South Africa
Intervention: Tenofovir vaginal microbicide
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Tenofovir vaginal microbicide			
HIV infection	135 per 1000	85 per 1000 (58 to 126)	RR 0.63 (0.43 to 0.93)	889 (1 study)	⊕⊕◯◯ low[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Only one small trial has so far assessed the tenofovir microbicide gel

DISCUSSION

Summary of main results

By the end of 2011, eight effectiveness and one proof-of-concept RCTs involving six different vaginal microbicides (SAVVY, CS, Carraguard, PRO 2000, BufferGel and tenofovir) and 31,941 sexually active women had either been conducted to term or stopped early at the recommendation of the respective DSMB. No trials have assessed the effect of topical microbicides during anal sex. The two trials that assessed the effectiveness of CS were stopped early due to safety concerns, and one 2% PRO 2000, one tenofovir and two SAVVY trials were stopped early because of insufficient rate of HIV infection and a low likelihood of showing a protective effect. The three trials conducted to term assessed the effectiveness of BufferGel and 0.5% PRO 2000, Carraguard and tenofovir. One proof-of-concept trial that enrolled 889 women suggested that a vaginal microbicide containing tenofovir may be effective in reducing the risk of acquisition of HIV and HSV infections. Effectiveness data are not yet available from the second tenofovir study that enrolled 5000 women and was stopped early due to a low likelihood of showing a protective effect. Other types of vaginal microbicides have not shown evidence of an effect on HIV or STI acquisition. Overall, there was no significant difference between microbicide and placebo groups in the incidence of adverse events.

Overall completeness and applicability of evidence

All eight completed trials reported HIV as the primary outcome; however, not all STIs were addressed by the individual trials. Only four trials assessed the effect of vaginal microbicides on other viral STIs (Abdool Karim 2010; McCormack 2010; Skoler-Karpoff 2008; Van Damme 2008). Four trials assessed vaginal microbicide effects on gonorrhoea (Halpern 2008; McCormack 2010; Skoler-Karpoff 2008; Van Damme 2008), four on chlamydia (Halpern 2008; McCormack 2010; Skoler-Karpoff 2008; Van Damme 2008), two on syphilis (Skoler-Karpoff 2008; Van Damme 2008) and two on trichomoniasis (Skoler-Karpoff 2008; Van Damme 2008). Most of the trials were stopped early due to safety concerns leading to high attrition rate and high risk of bias.

The relatively small sample size may restrict the broad generalisability of the finding that tenofovir reduces the risk of HIV and HSV-2 acquisition in sexually active women (Abdool Karim 2010). If the effectiveness of the tenofovir microbicide is confirmed in further studies, there will need to be a clear pathway to rapid regulatory approval. In addition, the successful launch of the effective gel will depend on having in place appropriate mechanisms for distribution to the women who need it, along with a strategy for ensuring that they use it correctly.

Quality of the evidence

Using the GRADE system (Guyatt 2011), we judged the quality of the currently available evidence to be low for both HIV and other STIs; as shown in Summary of findings for the main comparison. In particular, we judged the evidence that tenofovir reduces the risk of sexual acquisition of HIV to be low; mainly because of impression (resulting from the small sample size) and the absence of data on anal sex (Summary of findings 2). A GRADE rating of low-quality evidence indicates that "our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect" (Balshem 2011).

Potential biases in the review process

We minimised potential biases in the review process by adhering, as strictly as possible, to the guidelines of the Cochrane Collaboration (Higgins 2011). We conducted comprehensive searches of both peer-reviewed and grey literature; without limiting the searches to a specific language. Two independent review authors assessed study eligibility, extracted data and assessed the methodological quality of each included study.

Agreements and disagreements with other studies or reviews

This review is in agreement with other studies that (apart from the tenofovir microbicide trial in South Africa) topical microbicide research has had disappointing outcomes (Buckeit 2010; Cutler 2008; Garg 2009; Klasse 2008; Nuttall 2010; Wilkinson 2002a; Wilkinson 2002b). To the best of our knowledge, our review is the most comprehensive synthesis of existing evidence on topical microbicides for prevention of HIV infection.

AUTHORS' CONCLUSIONS

Implications for practice

At present, limited evidence suggests that vaginal microbicides containing tenofovir, a nucleotide reverse transcriptase inhibitor, may reduce HIV acquisition in heterosexual women; but other types of topical microbicides have not shown evidence of an effect on the acquisition of HIV infection or other STIs. Therefore, there is not enough evidence to recommend topical microbicides for HIV prevention at present. If the effectiveness of the tenofovir microbicide is confirmed in further studies, there will need to be a clear pathway to rapid regulatory approval. In addition, the successful launch of the effective gel will depend on having in place appropriate mechanisms for distribution to the women who need it, along with a strategy for ensuring that they use it correctly.

Limited evidence suggests that vaginal tenofovir microbicides may reduce the risk of acquisition of HIV and HSV-2 infections in women; but other types of topical microbicides have not shown evidence of an effect on HIV or STI acquisition. Therefore, there is not enough evidence to recommend topical microbicides for HIV or STI prevention at present. If the effectiveness of tenofovir or other microbicides is confirmed in further studies, there will need to be a clear pathway to rapid regulatory approval. Successful launch of the effective gel would depend on having in place appropriate mechanisms for distribution to the women who need it, along with a strategy for ensuring that they use it correctly.

Implications for research

Further studies are needed to confirm the beneficial effects of the tenofovir gel in vaginal sex. In addition, further research should continue on the development and testing of new topical microbicides.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abdool Karim 2010

Methods	A 2-arm, double-blind, randomised, placebo-controlled trial conducted from May 2007 to March 2010. Women were enrolled at an urban and a rural clinic in KwaZulu-Natal, South Africa. Enrolment took place from May 2007 to January 2009
Participants	Rural and urban HIV-negative women from KwaZulu-Natal, aged 18 to 40 years, who were sexually active (defined as having engaged in vaginal sex act at least twice in the 30 days prior to screening), not pregnant and using a non-barrier form of contraceptive. Exclusion criteria included those with a history of adverse reactions to latex, planning to either travel away from the study site for more than 30 consecutive days, relocate away from the study site, become pregnant, or enrol in any other behavioural or investigational product study. Participants who had a creatinine clearance < 50 mL/minute, had evidence of genital deep epithelial disruption, had in the past year participated in any research related to any vaginally applied product(s) or had an untreated STI or reproductive tract infection were also excluded 2160 women were screened and 1085 were enrolled, of whom 899 were included in the analysis
Interventions	INTERVENTION GROUP: 1% tenofovir gel and condom. Tenofovir gel comprised 40 mg of PMPA in a solution of purified water with edatate disodium, citric acid, glycerin, methylparaben, propylparaben and HEC CONTROL GROUP: Placebo gel (universal HEC gel) and condom Women were requested to insert 1 dose of gel in the 12 hours before sex and a second dose of gel as soon as possible in the 12 hours after sex and no more than 2 doses of gel in a 24-hour period. Follow-up comprised provision with comprehensive HIV prevention services (HIV pre- and post-test counselling, HIV risk reduction counselling, condoms and STI treatment), reproductive health services and provision of assigned study gel. Participants were requested to return their used and unused applicators at every visit. From October 2008, individualised, motivational interview was introduced to assess obstacles to gel use and set goals for optimal adherence in the upcoming month. The women were specifically and repeatedly counselled to only use the gel vaginally and the lack of safety with rectal use was highlighted. Each participant had monthly HIV and urine pregnancy testing performed before gel was dispensed. Self-reported data on gel use and sexual frequency during the last 30 days were collected at monthly visits, together with gel and condom use on the day of the last sex act, by means of a brief interviewer-administered questionnaire. 2 months after study exit, participants attended a post-trial visit to assess HIV status and safety after product withdrawal. Drug safety was assessed at every study visit by evaluating, grading and recording adverse events experienced by participants. Participants underwent quarterly pelvic examinations and, if needed, colposcopy. Serology was performed for hepatitis B virus and HSV-2 virus. Haematological, hepatic and renal abnormalities were assessed at study months 3, 12 and 24, additionally when clinically indicated, and at study exit. Adverse events were graded for severity via the Division of AIDS Table for Grading Adult and Pediatric Adverse Events, 2004. Product use was temporarily discontinued for an adverse event at the discretion of the study clinician. When HIV seroconversion was established, product use

	was discontinued and women were referred to local AIDS treatment services, including the CAPRISA AIDS Treatment Programme, which provides free ARV therapy. The visits took place monthly for 30 months
Outcomes	HIV status established by 2 HIV rapid tests, Determine HIV 1/2 and Uni-Gold Recombigen® HIV test were performed at each study visit. Participants with concordantly positive, discordant or indeterminate results were assessed for possible seroconversion by 2 separate RNA PCR assays, about 1 week apart. Stored plasma, available from prior study visits by each seroconvertor was tested by RNA PCR to identify the window period for HIV infection (RNA PCR positive but rapid HIV test negative) at prior visits
Notes	The study was approved by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (E111/06), FHI's Protection of Human Subjects Committee (#9946) and the South African Medicines Control Council (#20060835). Participants signed informed written consent The relatively small sample size may restrict the broad generalisability of the results of this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as "using permuted block randomisation of sizes 12 and 18, with no stratification, to 1 of the 6 codes"
Allocation concealment (selection bias)	Low risk	Participants assigned a sequential identification number, which corresponded to a unique envelope (accessible only to each study site pharmacist) that allocated her randomly using permuted block randomisation of sizes 12 and 18, with no stratification, to 1 of 6 codes. The 3 codes assigned randomly to each of tenofovir and placebo gels were held in confidence by the product manufacturer and independent Data Safety and Monitoring Board (DSMB) statistician
Blinding (performance bias and detection bias) All outcomes	Low risk	Tenofovir and placebo gels appeared identical and were dispensed in the same prefilled vaginal applicators with identical packaging
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up (2.8%), withdrawal during follow-up (1.3%), withdrawn for sharing study product (0.3%), withdrawn for co-enrolling in another microbicide trial af-

Abdool Karim 2010 (*Continued*)

		ter enrolment in CAPRISA 004 (0.3%), relocation (0.2%), deaths (0.1%)
Selective reporting (reporting bias)	Low risk	The study protocol stated that HIV incidence was the primary outcome
Other bias	Low risk	No other potential sources of bias

Abdool Karim 2011

Methods	Randomised, placebo-controlled trial with 3 double-blinded gel arms and 1 open-label no gel arm in Malawi, South Africa, Zambia, Zimbabwe and the US. Women were randomly assigned in equal proportions to 1 of the 4 study arms. Randomisation was stratified by site in blocks of size 12 or 24, distributed randomly. Each random sequence was determined through generation of uniform random variates in a computer program (SAS; Statistical Analysis System Institute Inc., Cary, North Carolina, US). The trial was conducted between February 2005 and January 2009
Participants	3101 HIV-negative non-pregnant women, at least 18 years of age, who were sexually active, defined as having had vaginal intercourse at least once in the past 3 months, and able to provide adequate contact information to study officials for purposes of follow-up. Exclusion criteria included those with a history of adverse reactions to latex, use of non-therapeutic injection drugs in the past 12 months and a history of vaginal intercourse more than an average of twice per day in the past 2 weeks, planned to become pregnant in the 30 months after study entry, planned to travel away from the study site for more than 3 consecutive months in the 30 months after study entry, planned to relocate away from the study site in the 30 months after study entry, participation in another clinical trial of a vaginal product, pregnant within 42 days of study entry, had an STI or other reproductive tract infection diagnosed by the study staff, abnormal pelvic examination indicating deep epithelial disruption, condition that in the opinion of the investigator may interfere with the study, liver or kidney function abnormality of grade 3 or higher, blood or blood clotting abnormality of grade 4 or higher 5888 women were screened and 3101 enrolled and randomised
Interventions	INTERVENTION GROUP: BufferGel and 0.5% PRO2000 CONTROL GROUP: placebo gel (HEC gel) Participants were given single-use, prefilled applicators of gel and requested to insert 1 applicator of gel intravaginally up to 1 hour before each episode of vaginal intercourse. Study gels were similar in appearance and were packaged in identical vaginal applicators
Outcomes	**Primary outcome:** **1)** Safety was assessed by deep epithelial disruption, other genital symptoms or other systemic symptoms. Local mucosal toxicity was assessed by the incidence of deep epithelia disruption, observed on pelvic examination (speculum, colposcopic or both) as lesions penetrating into and exposing the subepithelial tissue and possibly blood vessels. Additional safety outcome included adverse genital signs and symptoms, as well as haematological hepatic, and renal abnormalities of grade 3 or higher severity based on the Division of AIDS Table for Grading Adult and Paediatric Adverse Events, 2004

	2) HIV infection as measured by seroconversion. At the US site, the OraQuick ADVANCE HIV 1/2 antibody test was used. In the African sites, 2 rapid tests were used; the Determine HIV 1/2 test was used with either the OraQuick or Uni-Gold Recombigen® HIV test. The Zambia site used only the OraQuick assay during follow-up Western blot was performed on samples with any positive HIV result. If the Western blot result was indeterminate or positive, a second blood sample was collected (approximately 2 weeks later) for further Western blot testing. If the second Western blot result was positive, HIV infection was considered confirmed. For women who tested HIV-positive in their first follow-up visit, plasma stored at study entry was tested by an RNA-PCR to identify women who may have been in the window period of acute HIV infection at enrolment **Secondary outcome: i**ncidence of STIs (as per protocol). Test details not available
Notes	The study was approved by 11 institutional review boards that oversee research conducted at 8 study sites, as well as regulatory authorities in the US, South Africa and Zimbabwe. All participants demonstrated adequate understanding of the trial and provided written informed consent

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by site in blocks of size 12 or 24, distributed randomly. Each random sequence was determined through generation of uniform random variates in a computer program (SAS; Statistical Analysis System Institute Inc., Cary, North Carolina, US)
Allocation concealment (selection bias)	Low risk	Within each block of size 12 (24), 3 (6) assignments to each of the 4 treatment arms were allocated in random order. For the 3 gel arms, each of the 3 assignments within a block was associated with a unique 3-digit code that was labelled on the product packaging. In blocks of size 24, each unique 3-digit code was used twice. Envelope materials were created and sealed at the SDMC. Upon enrolment of a participant at each site, clinic staff opened an envelope revealing assignment to any gel group or to no gel. For those assigned to any gel group a corresponding envelope was opened only by the pharmacist to reveal the 3-digit code of the product to be prescribed

Abdool Karim 2011 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	All the study gels were similar in appearance and were packaged in identical vaginal applicators. All people associated with the study were masked to the product identity of the 3-digit codes throughout the course of the trial, except for the product manufacturers and 1 independent statistician at the SDMC (not associated with the trial)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up was about 5% in each group and was either due to loss of contact, participation refusal, relocation, death or other unknown factors
Selective reporting (reporting bias)	Low risk	The study protocol stated that safety and HIV infection were the primary outcomes. Secondary outcomes included incidences of STIs, pregnancy, acceptability, rate of condom use versus gel use and establishment of a repository of vaginal swab specimens for long-term storage and future research testing on biomarkers of microbicide safety and effectiveness
Other bias	Low risk	No other potential sources of bias suspected

Feldblum 2008

Methods	Double-blind, randomised, placebo-controlled trial in Lagos and Ibadan in Nigeria. Enrolled participants were randomised to either treatment groups using a 1:1 allocation ratio. The trial was conducted between September 2004 and December 2006. Participants were recruited from local market areas, bars, hostels, military barracks and colleges, but not brothels
Participants	2153 women aged 18 to 35 years, who were HIV-negative, non-pregnant, reported more than 2 coital acts per average week, more than 1 sex partners in the last 3 months and willing to use vaginal gel and condoms for 12 months. Exclusion criteria were women who were pregnant, HIV positive or both
Interventions	INTERVENTION GROUP: 1.0% C31G (SAVVY) gel and condom CONTROL GROUP: HEC (placebo) as the gelling agent and sorbic acid as preservative Both gels were similar in appearance (clear viscous) dispensed in 3.5-mL doses with applicator and had pH 4.4. Participants were instructed to use the vaginal gels before the act (and insert a second time if more than 1 hour had elapsed between the first application and sexual intercourse). Frequency and administration of the gels were similar. Participants were instructed on proper condom use and gel application and were asked to return for more condoms and gel if needed. They were counselled to use condoms at every coital act, that gel effectiveness was unknown and that they may be receiving a

	placebo gel that is known not to protect against HIV Follow-up comprised of answering structured questionnaires including information on recent sexual behaviour, condom and gel use and medical problems or medication use since the previous visit. Participants underwent pregnancy and HIV rapid testing and STI risk-reduction counselling and received a 1-month supply of condoms and study gels. At the 6-month follow-up visit, participants returned to the main study clinic for pelvic, STI and saline wet mount examination of a vaginal specimen. Those who became pregnant were discontinued from product use, but remained in the study for monitoring, HIV testing and other data collection and assessment of pregnancy outcome. If pregnancy ended during follow-up, a participant could start product use. Those confirmed to be HIV positive were discontinued from the study and referred to the PEPFAR treatment programmes for care and ARV therapy if needed. Any adverse event reported was referred to the study clinic for evaluation and STI testing as needed. If a participant missed a scheduled follow-up appointment, up to 3 attempts were made to contact her and her file remained open until study closeout. The visits took place monthly for 12 months
Outcomes	Incidence of HIV infection; indicated by detection of HIV antibodies in OMT (rapid test) or blood (ELISA) and confirmed by Western blot or PCR testing
Notes	The study was approved by the University of Ibadan, the Nigerian Institute of Medical Research, and the Protection of Human Subjects Committee, FHI (US). Participants signed written informed consent. Supported by funds from the USAID. Investigational products donated by Cellegy Pharmaceuticals. Participants provided written informed consent Study was prematurely terminated in August 2006. The DSMB recommended that the study be stopped because the HIV incidence was less than half the expected rate. It was estimated that the study needed to enrol approximately 1980 additional participants to identify the number of HIV infections that would offer the desired study power

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation sequence generated using a computer random number generator
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed opaque envelopes were used to assign participants to 1 of 6 colour groups. The randomisation envelopes were maintained in a secure office and were not available to study staff until the moment of randomisation. Allocation done using randomly varied permuted-blocks of size 12, 18 and 28 stratified on site
Blinding (performance bias and detection bias) All outcomes	Low risk	6 label colours (3 SAVVY and 3 placebo) were used to differentiate the otherwise identical packaged gels. Participants, field

Feldblum 2008 (*Continued*)

		study staff, monitors, statisticians and other staff involved in the trial were not aware of which gel colours were associated with SAVVY or placebo. Each randomisation envelop was used only once. Both SAVVY and placebo gels were clear with similar viscosity and pH, dispensed in 3.5-mL doses with identical applicators
Incomplete outcome data (attrition bias) All outcomes	Low risk	6.3% in the intervention group and 7% in the control arm were discontinued due to early termination Early discontinuation due to seroconversion (1.5%) and lost to follow-up (11.7%) were similar in both the intervention and control groups Primary analysis - ITT with modifications: randomised participants later found to be positive for HIV at enrolment were excluded from analysis; for STI outcomes, women who were positive for STI at enrolment started their time in analysis on their first negative STI test following treatment
Selective reporting (reporting bias)	Low risk	HIV incidence was the outcome stated in the protocol
Other bias	Low risk	Trial stopped early for data-dependent processes, but we do not think that this could have introduced bias to the study

Halpern 2008

Methods	Double-blind, randomised, placebo-controlled trial conducted between November 2004 and March 2007 in Lagos and Port Harcourt, Nigeria. Women were recruited from bars, market and other common gathering areas and potential study participants referred to study clinics for screening. 1644 women were enrolled into the trial
Participants	1644 women aged 18 to 35 years HIV-antibody negative, who on average have 3 or more acts of intercourse per week and more than 1 sexual partner in the last 3 months. Tested for syphilis, gonorrhoea, chlamydial infection and pregnancy at enrolment, treated and admitted to the study Exclusion criteria: pregnancy, HIV positive, participation in another microbicide trial, less than 3 months since their last pregnancy or desire to become pregnant in the next 12 months and drug injection use. Most study participants were low-income women who exchange sex for money to supplement their income, although they did not exclusively act as sex workers

Interventions	INTERVENTION GROUP: CS and condom. Each 3.5-mL application of 6% CS gel contained 231 mg of the active ingredient, sodium CS. The CS had a pH of 7.5 CONTROL GROUP: placebo gel and condom. The gel contained HEC as gelling agent, no cell toxicity or anti-HIV properties, and had a pH of 4.4 Both CS and placebo were administered in a 3.5-mL dose via a plastic single-use applicator. Participants were instructed to insert the contents of 1 full applicator of their assigned gel into the vagina immediately prior to each act of sexual intercourse throughout the 12 months of study participation and re-apply the gel if intercourse did not take place within 1 hour after application. Participants were instructed to use condoms for all acts of sexual intercourse regardless of gel use, not to douche after sex, not to use any other vaginal products and not to use the study gel in anal intercourse. Referral information was provided for local family planning clinics, when participants expressed interest in using contraceptives other than condoms. Women diagnosed with gonorrhoea, chlamydia, trichomoniasis, syphilis, candidiasis or bacterial vaginosis during screening or enrolment were treated and admitted to the study Follow-up visits were held every month for 12 months, and comprised an interview (health, any adverse experiences, concomitant medication use since last visit, coital frequency, gel and condom adherence in the last 7 days), testing for HIV, gonorrhoea, chlamydia, and demonstration of gel and condom use, and risk reduction and adherence counselling. Participants were encouraged to return for re-supply of condoms and gels if they ran out between their scheduled visits. Women presenting with adverse events were referred to the clinic for evaluation and treatment and those who became pregnant stopped using the product until the pregnancy had ended. To avoid social stigma, those who seroconverted were not discontinued from the study, and were not required to stop gel use so they could continue contributing the STI and safety outcomes. All HIV-infected participants were referred to appropriate local facilities for social support and clinical management, including ARV drugs if indicated
Outcomes	Primary outcome: incidence of HIV-1 and HIV-2 infections. This was determined by antibodies in OMT using Advance Rapid HIV-1/2 antibody test and confirmed by Western blot. For women who seroconverted during the first 3 months of follow-up, qualitative RNA-based PCR testing for HIV was performed on stored enrolment plasma to assess whether the infection was pre-existing. PCR testing for HIV was also conducted on final visit plasma samples to identify recent infections in the absence of antibodies Secondary outcomes: incidence of STI (gonorrhoea or chlamydial infection). This was measured by detecting DNA material in self-administered vaginal swabs using the SDA assay
Notes	The trial received ethical approval from the College of Medicine, University of Lagos; the University of Port Harcourt Teaching Hospital and FHI. Written informed consent was required and measures were put in place to ensure the process was adequate for illiterate participants. Informed consent was obtained. Funded by USAID and CONRAD Premature stoppage: an unplanned interim safety analysis was conducted in January 2007 after an apparent increased risk of HIV in the CS arm was found in a parallel trial (Van Damme 2008). The DSMB found no increased HIV risk in the CS arm of this study but recommended that the trial be stopped due to safety concerns arising from the results of the parallel trial (Van Damme 2008). Last follow-up visit was in March 2007

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A statistician not involved in the study developed the allocation sequence using a stratified (by study site) randomly permuted block design with block sizes 12, 18 and 24" Comment: we assume sequence was generated by computer
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes were used to assign participants to 1 of the 6 colour groups after they signed the enrolment consent form and were determined eligible for the study
Blinding (performance bias and detection bias) All outcomes	Low risk	6 product label colours (3 for CS and 3 for placebo) were used to improve blinding. Therefore, revealing 1 colour would not unblind the entire study. There was no indication that any unblinding occurred during the study. Both CS and placebo gels were identical in packaging and labelling
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up: 30% (242/820) in the intervention and 30% (247/824) in the control group Early discontinuation: 0.1% in each group Excluded from effectiveness analysis: 9% from the intervention group and 8% from the control group, including those with no follow-up on HIV test and those who were HIV PCR positive All primary analyses were performed on an ITT basis
Selective reporting (reporting bias)	Low risk	HIV incidence, gonorrhoea and chlamydial infections were the stated outcomes in the protocol
Other bias	Low risk	Trial stopped early for data-dependent processes, but we do not think that this could have introduced bias to the study other than attrition bias as indicated above

McCormack 2010

Methods	Randomised, double-blind parallel group trial. Participants were enrolled at 13 clinics, which were managed by 6 research centres in Africa. 3 were in South Africa (Chris Hani Baragwath Hospital, Bertsham; Africa Centre for Health and Population Studies, Mtubatuba; HIV Prevention Research Unit, Medical Research Council, Westville), 1 in Mwanza, Tanzania (AMREF Lake Zone Programme), 1 in Entebbe, Uganda (MRC Programme on AIDS in Uganda, Uganda Virus Research Institute) and 1 in Mazabuka, Zambia (MDP Zambia, Nakambala Sugar Estate). Participants were randomly assigned in a 1:1:1 ratio to 2% PRO 2000, 0.5% PRO 2000 or placebo groups on the basis of the lists that were created with randomised permuted blocks of varying sizes for each of the 13 clinics, by an independent statistician with a computerised random number generator, containing unique trial numbers matched to 9 sets of study product codes. 9385 women were enrolled. The study was conducted from September 2005 to August 2008
Participants	9385 women aged 18 years or older (> 16 years in Tanzania and Uganda), who did not have HIV-1 infection at screening and were willing to have regular speculum examinations and urinary pregnancy tests, were willing to use gel as instructed, were likely to be sexually active, were willing to receive health education about condoms, and were willing and able to give informed consent. Exclusion criteria included women who were unable or unwilling to provide a reliable method of contact, were likely to move out of the area within 12 months, were likely to have sex more than 14 times a week on a regular basis (a regulatory requirement was that no more than 60 applicators were to be dispensed at every 4-weekly visit), used spermicides regularly, were pregnant or within 6 weeks' post partum, had a severe clinical or laboratory abnormality, needed referral for assessment of a suspicious cervical lesion, had received treatment to the cervix or other gynaecological procedure within 30 days of enrolment, were allergic to latex, or were participating or had participated in another clinical trial that was likely to affect the primary efficacy end point within 30 days before enrolment
Interventions	INTERVENTION GROUP: 2% PRO 2000 and 0.5% PRO 2000 gels and condom CONTROL GROUP: HEC placebo gel and condom Gel was dispensed in identical applicators, in packs of 10 prefilled single-dose applicators (maximum of 60 applicators in 10 packs per visit). Women were instructed to apply gel within 1 hour before sexual intercourse. They were counselled to use condoms during all sex acts and received unrestricted supplies of free condoms at the research clinics. Follow-up at every 4-week visit, women were asked about gel and condom use at the most recent sex act and returned used and unused applicators, which were counted and recorded for assessments of adherence. HIV-1 status was assessed at 12, 24, 40 and 52 weeks (up to 104 weeks in Uganda). The study product gels and condoms were re-supplied during the visits. A clinical interview, pelvic examination to report genital and non-genital adverse events and urinary pregnancy tests were done at these visits. Routine haematology and biochemistry tests were done for the first 500 participants enrolled in centres in Durban and Johannesburg, South Africa, and all 840 participants in Uganda at screening, and at 12, 24 and 52 weeks (and 104 weeks or at final visit in Uganda). A plasma sample was obtained from all these participants at the final visit for PRO 2000 analysis
Outcomes	HIV-1 infection: the HIV testing algorithm comprised parallel HIV-1 rapid tests, with discordant or positive tests after enrolment triggering ELISA testing. A second serum sample was obtained at the subsequent visit after a first positive rapid test result. The algorithm was designed to confirm HIV-1 infection on the basis of 2 separate samples

	with 2 different methods of diagnosis. Serum samples were tested for HIV-1 antibodies with fourth-generation and third-generation ELISAs, and Western blot assay. HIV-1 antigen ELISA was used as a confirmatory assay for p24 testing. Buffy coat samples were tested using DNA PCR. Roche COBAS Amplicor was used for detection of HIV-1 RNA if the buffy coat specimen was not satisfactory HSV-2 established serologically and confirmed by central laboratory at 40 and 52 weeks *Neisseria gonorrhoeae* or *Chlamydia trachomatis* established by a positive nucleic acid amplification assay at 24 weeks
Notes	The protocol was approved by local and national ethics committees, in all participating countries and in the UK. Authorisation was obtained from the national regulatory authority in all participating countries and the US Food and Drug Administration. Participants provided written informed consent or witnessed thumbprint. Enrolment on protocol; 9404. Funding provided by UK Department for International Development, UK Medical Research Council, European and Developing Countries Clinical Trials Partnership, IPM and Endo Pharmaceuticals Solutions The 2% PRO 2000 gel was discontinued early (14 February 2008) after a review by the DSMB, which advised there was little chance of the 2% gel showing benefit given the planned sample size and postulated effect size. However, the conditional power for significant benefit from the 0.5% PRO 2000 dose (based on the original sample size assumptions) was sufficiently high to warrant trial continuation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated with a computerised random number generator
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned in a 1:1:1 ratio to 2% PRO 2000, 0.5% PRO 2000 or placebo groups on the basis of the lists that were created with randomised permuted blocks of varying size for each of the 13 clinics At enrolment, women were assigned a unique trial number selected sequentially from the clinic trial register
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators and participants were masked to group assignment. Site pharmacists dispensed gel in identical applicators on the basis of the trial number and the assigned study product codes on the clinic randomisation list. Only statisticians responsible for the preparation of the DSMB reports and essential manufacturing and distribution staff had access to the list matching study product codes to gel. No other site person-

McCormack 2010 (*Continued*)

		nel had access to the list
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up (6.9%), withdrawals (3. 0%), discontinued gel use (3%), interrupted gel use (5.9%) The primary efficacy analysis comprised all enrolled participants, excluding those with HIV-1 infection at enrolment (0.7%) , those without follow-up data (4.9%), and with censoring at 52 weeks (plus 6-week window for final visit) and while gel was discontinued because of pregnancy
Selective reporting (reporting bias)	Low risk	The study protocol stated that the primary efficacy end point was HIV-1 infection, and secondary efficacy end points were acquisition of HSV-2, presence of *Neisseria gonorrhoeae* or *Chlamydia trachomatis*
Other bias	Low risk	Trial stopped early for data-dependent processes, but we do not think that this could have introduced bias to the study

Peterson 2007

Methods	Double-blind, randomised, placebo-controlled trial conducted between March 2004 and February 2006 in Accra and Kumasi, Ghana. 2142 women were enrolled into the trial after recruitment from areas within each city that were considered high HIV transmission areas, including markets, bars and hotels
Participants	2142 women aged 18 to 35 years who were at risk of HIV infection, HIV-antibody negative, non-pregnant, agreed to use the study gel as directed and follow study participation and report self-medication with antibiotics during study procedures, and avoid use of spermicides or other vaginal contraceptives or lubricants during the study Exclusion criteria included women who were intending pregnancy, had a history of latex allergy, were injection drug users or had gynaecological conditions that could affect the safety or effectiveness of the study gel
Interventions	INTERVENTION GROUP: 1% C31G (SAVVY) and condom CONTROL GROUP: HEC (placebo) as the gelling agent and sorbic acid as preservative Both gels were similar in appearance (clear, viscous), dispensed in 3.5-mL doses with applicator and had a pH of 4.4. Participants were instructed to use the gels vaginally before each act of sexual intercourse (and to insert a second dose if more than 1 hour had elapsed between the first application and sexual intercourse) and to use condoms for all sexual contacts with all partners At each monthly follow-up visit, participants underwent OMT, HIV and pregnancy testing, adverse events assessment, STI risk reduction counselling, and study product and condom re-supply. They responded to structured questionnaires on their interval sexual

	behaviour (including coital activity and gel and condom use), experience using the gel, and were reminded of study concepts discussed during the informed consent process. If clinically indicated, participants underwent physical examination and STI testing. Study staff documented whether product use was interrupted temporarily or permanently for any of the following reasons; participants ran out of supplies, investigator withdrew study product in the interest of the safety and well-being of the participant, positive pregnancy test result or confirmed HIV infection. Pregnant women were allowed to resume study product use after pregnancies had ended. Those who became infected with HIV during the study were referred to local HIV-related psychological, social and medical services (such as viral load, CD4 level and HIV resistance testing) as well as ARV drug therapy when needed. If a participant missed a scheduled follow-up appointment, up to 3 attempts were made to contact her and her file remained open until study closeout. The visits took place monthly for 12 months
Outcomes	Incidence of HIV-1 and HIV-2, measured by detecting antibodies in ORT (Rapid HIV-1/2 test) and confirmed by ELISA, Western blot or both
Notes	The study protocol was approved by the Committee on Human Research, Publications and Ethics, School of Medical Sciences, University of Science and Technology, Kumasi, Ghana; Noguchi Memorial Institute for Medical Research IRB, University of Ghana, Legon, Ghana; and the Protection of Human Subjects Committee FHI, US. Written informed consent was required Supported by funds from the USAID. Investigational products donated by Cellegy Pharmaceuticals The study was stopped prematurely (November 2005) following recommendations of DSMB because the HIV incidence among enrolled participants was substantially lower than expected. The study statistician estimated that approximately 3500 additional participants (beyond the 2124 planned sample size) would be needed to achieve the required number of HIV infections

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated using a computer random number generator
Allocation concealment (selection bias)	Low risk	Randomisation done using randomly varied permuted blocks of 12, 18 and 24; stratified by study site. Sequentially numbered sealed opaque envelopes were used to assign participants to 1 of the 6 colour groups after they qualified for the study and signed the consent form
Blinding (performance bias and detection bias) All outcomes	Low risk	6 label colours (3 SAVVY and 3 placebo) were used to differentiate the identically packaged gels. The randomisation envelopes were maintained in secure office

		and were not available to study staff until the moment of randomisation. Each randomisation envelope was used only once. Participants, field study staff, monitors, statisticians and other FHI staff involved in the trial were not aware of which gel colours were associated with SAVVY or placebo. Both gels had similar appearance (clear, viscous), pH and were dispensed in 3.5-mL doses with identical applicators
Incomplete outcome data (attrition bias) All outcomes	High risk	Due to premature termination of the study, 15.6% in the intervention and 15.2% in the control group exited the study before completing their 12th month visit. Loss to follow-up was 6.7% in the intervention and 7.8% in the control group 0.3% in each treatment group were discontinued early The evaluable population included the same participants as the effectiveness population, but excluded all data collected after the first documented interruption of product use
Selective reporting (reporting bias)	Low risk	Incidence of HIV-1 or HIV-2 infection was the main outcome stated in the protocol
Other bias	Low risk	Trial stopped early for data-dependent processes, but we do not think that this could have introduced bias to the study other than attrition bias mentioned above

Skoler-Karpoff 2008

Methods	Randomised, double-blind, placebo-controlled trial conducted between March 2004 and March 2007 in 3 South African sites (University of Cape Town; University of Limpopo, Medunsa campus, Ga-Rankuwa; and Medical Research Council, Durban). Women were recruited from local health clinics, malls (shopping centres), churches, taxi ranks and other community venues A substudy assessed the association of HR-HPV in women at study end and Carraguard use. Participants entered the HR-HPV study in October 2006, 6 months before the study end
Participants	6202 women aged 16 years and older, sexually active, HIV-negative. Exclusion criteria: a desire to become pregnant in the next 2 years at the time of screening, within 4 weeks of last pregnancy outcome at time of enrolment, had a Pap smear at screening grades as carcinoma, injected illicit drugs in the 12 months before screening or were participating in any other clinical trial or HIV prevention study. Those with abnormal Pap smears

	were referred for colposcopy 1723 women were included in the HR-HPV substudy
Interventions	INTERVENTION GROUP: Carraguard gel and condom CONTROL GROUP: methylcellulose (placebo) gel and condom Both gels were packaged in single-use microlax-type applicators, each filled with 7 mL of gel to dispense approximately 4 mL. Appearance and frequency of administration of the gels were similar. Clinicians provided instructions for gel use to participants, who then inserted the initial dose of study gel under supervision in the clinic. Participants were instructed to vaginally insert the study gel up to 1 hour before every act of vaginal intercourse, use condoms together with the gel and not to insert any other vaginal products (apart from the medication prescribed by study clinicians) Follow-up visits were every 3 months for up to 2 years (a minimum of 9 months and a maximum of 24 months). The visits comprised HIV testing, pelvic examination with speculum, pregnancy test, counselling on HIV reduction, family planning, ongoing informed consent, behavioural interview (women reported the number of vaginal sex act and whether they had used the study gel or condom during the last sex act) with clinic staff. When clinically indicated, women were tested for curable STIs including chlamydia, gonorrhoea, syphilis and trichomoniasis, which were treated syndromically. Testing and treatment for vaginal infections (bacterial vaginosis and yeast) was done if women were symptomatic. Pap smears and physical examinations were undertaken yearly. Women with abnormal Pap smears were referred for colposcopy. Those who tested positive for HIV or pregnancy were discontinued per protocol and referred to local services in trial communities. Participants were instructed to return all used and unused applicators at every visit. Applicators returned opened were sprayed with a solution that reacts to mucous and stains blue in a characteristic pattern if an applicator was inserted into the vagina (97.5% sensitivity, 96% specificity). Participants who seroconverted at month 1 or 3 had their baseline samples tested to establish their HIV serostatus at enrolment with HIV PCR DNA or RNA PCR detection or both Samples for HPV detection were collected once from consenting women at the Carraguard phase III trial closeout visit. A measure of compliance was added to the HPV substudy. There were 2 candidates for the measure of treatment compliance. The insertion of > 80% of opened, returned applicators determined by applicator staining, which detected whether the applicator had been inserted into the vagina. The other measure was the percentage for covered sex acts, which was calculated by dividing the average number of applicator insertions (confirmed by applicator staining) by the average number of reported sex acts. Since applicator insertion was verifiable while the denominator used to calculate covered sex acts was not verifiable, applicator insertion was selected as the basis for the measure of compliance. There were 426 women (215 Carraguard users and 211 placebo users) who inserted 80% of their opened returned applicators. Unfortunately, despite having claimed insertion of 80% of applicators, many of these women did not cover a substantial number of their sex acts. Sample size calculation indicated that a sample of 352 women would provide 80% power to detect a 50% difference between the treatment groups in the number of HPV-positive women at the end of the study. Based on sample size calculations it was known that approximately 175 subjects were needed, in each of the treatment groups in order to have sufficient power to obtain statistically significant results. In order to obtain this many 'truthful' subjects for analysis, the authors were forced to select 30% covered sex acts as the lower bound for compliance.

	In essence, women who were only 30% compliant with respect to covered sex acts were not as compliant as the authors would have preferred, but in order to have sufficient statistical power to detect a difference they had to accept this compromise. Restricting the definition of compliant (high adherence to gel use) subjects to 'women who inserted > 80% of their returned, opened applicators and covered 30% of their sex acts' provided a sample of 348 women (174 Carraguard users and 174 placebo users). The median per cent covered sex acts for this group was 58% as opposed to 50% for the 426 women who inserted > 80% of their returned, opened applicators. For these reasons, 'women who inserted > 80% of their returned, opened applicators and covered > 30% of their sex acts' was selected as a measure of adherence
Outcomes	Time to HIV seroconversion: HIV infection was diagnosed with 2 different rapid tests for detection of HIV antibodies, OraQuick ADVANCE HIV 1/2, Determine HIV 1/2 or Uni-Gold Recombogen®, which was done concurrently. Positive or discordant HIV rapid tests (sensitivity ranging 98% to 99% and specificity 98% to 99% as validated in the trial population) were confirmed by third-generation ELISA or by HIV PCR RNA *Neisseria gonorrhoea* and *Chlamydia trachomatis*: determined by PCR tests Syphilis: RPR with TPHA, IgG and IgM or BD Macro-Vue RPR Card tests Bacterial vaginosis and yeast infection: determined by wet mount and Whiff test. *Trichomoniasis vaginalis*; determined by culture HR-HPV: detected using Digene Hybrid Capture 2 analysis
Notes	The study was reviewed and approved by the Population Council Institutional Review Board, NY, US, the University of KwaZulu-Natal Biomedical Research Ethics Committee for the Medical Research Council; the University of Limpopo, Medunsa Campus, Research, Ethics and Publications Committee; the University of Cape Town Research Ethics Committee; and the South African Medicines Control Council, and was undertaken in accordance with the declaration of Helsinki. Participants gave written informed consent Funding: US Agency for International Development, Bill and Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	With use of a pseudo-random number generator available as part of the SAS software package (version 9.1), a statistician not connected with the trial or subsequent analysis (PharmaGuru, New Jersey, US) produced a block randomisation scheme, which was stratified by site, assigning participants to gel (Carraguard) or gel B (placebo)
Allocation concealment (selection bias)	Low risk	Assigned 25 barcodes to Carraguard and 25 barcodes to the placebo, which were printed on the applicators and boxes. Barcode numbers and the corresponding gel assignments were then loaded into a cus-

		tomised electronic barcode system, which was developed to enable randomisation, tracking of the gel shipments, and the distribution and returns of applicators from participants. Upon gel receipt, clinic staff scanned every box of gel into the MRPS system designated for all participants according to predetermined randomisation scheme and indication from which storage location the gel would be retrieved. Before dispensing, every box was scanned to verify that the boxes were from the correct barcode group
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the Carraguard and its matching placebo were packaged in single-use Microlax-type applicator each filled with 7 mL to dispense approximately 4 mL. To maintain blinding, only 2 non-clinical staff members at the Population Council, who were not involved in daily procedures, data cleaning or analysis, had access to records showing which barcodes corresponded to Carraguard or placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Early withdrawal comprised 8.7% in the intervention group and 9.2% in the control group Loss to follow-up was 7.1% in the intervention group and 6.7% in the control group. Loss due to death was similar (0.2%) in each group
Selective reporting (reporting bias)	Low risk	Incidence of HIV was the primary outcome stated in the protocol. Other outcomes reported included STIs (chlamydia, gonorrhoea, syphilis, trichomoniasis) and vaginal infections (bacterial vaginosis and yeast)
Other bias	Low risk	No other potential sources of bias

Van Damme 2008

Methods	Randomised, double-blind, placebo-controlled trial involving 3 African (South Africa, Uganda, Benin) and 2 Indian (Chennai, Bangalore) sites. The trial was conducted between July 2005 and March 2007. A total of 2985 women were screened of whom 1428 were enrolled into the trial
Participants	1428 women, aged at least 18 years old, negative HIV-antibody test, had an average of at least 3 acts of vaginal intercourse per week, have had at least 3 different partners in the previous 3 months, and agree to come to the clinic for 12 monthly follow-up visits. Exclusion criteria included an allergy to latex or spermicides, pregnancy or wanted to become pregnant in the next year, intravenous drug users, participation in another trial, had already been screened for this trial, or had any condition that made her participation unsafe or that the investigator believed could complicate interpretation of the data
Interventions	INTERVENTION GROUP: 6% CS gel and condom. CS had a pH of 7.5 CONTROL GROUP: placebo gel and condom. The placebo gel had a pH of 4.4 The gels were identical in appearance, delivered in 3.5-mL single-use opaque applicators and frequency of administration was similar. Women were asked to insert the gel into their vagina within 1 hour before each act of vaginal intercourse, during a period of 1 year. 12 monthly follow-up visits comprised counselling about reducing the risk of HIV infection, free condoms and treatment for curable STIs according to local guidelines. Women testing positive for pregnancy at 1 of their monthly visits had the product withdrawn until the pregnancy ended but did not discontinue the trial. Patients in whom seroconversion occurred were referred for care either within the study clinic or at an outside hospital
Outcomes	Primary: incidence of HIV-1 and HIV-2: determined by the presence of HIV antibodies in blood samples and PCR test for HIV RNA. If seroconversion occurred within 3 months after enrolment, a PCR test for HIV RNA was performed on an enrolment sample to confirm HIV status at baseline. A participant was considered to be infected if 2 of 3 rapid tests (Determine HIV 1/2, SD Bioline HIV 1/2, Uni-Gold HIV Recombinant) performed consecutively on the same blood sample were positive or if there was a positive PCR result at her final visit Secondary: incidence of gonococcal or chlamydial infection: determined by a positive test for SDA in cervical swab
Notes	The study was approved by the Institutional Review Board of the Eastern Virginia Medical School and by local ethical committees at the sites where women were recruited. Written informed consent was required Supported by grants from the Uited States Agency for International Development and the Bill & Melinda Gates Foundation The trial was stopped prematurely after the Independent Data Monitoring Committee determined that CS gel may have increased the risk of HIV infection as compared with placebo. In January 2007, sites were instructed to withdraw the product as soon as possible. Last follow-up visit was in March 2007

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"Participants were assigned to the six colour groups in equal ratios on the basis of a permuted-block randomisation scheme with stratification according to clinic, with random block sizes of 12, 18, and 24". The colours associated with each gel group were randomly assigned by a person not otherwise involved in the study, using a validated SAS software program (SAS Institute). Comment: w e assume from this description that the sequence was computer generated
Allocation concealment (selection bias)	Low risk	To conceal the group assignments, they were contained within sequentially numbered, sealed opaque envelopes that were kept in a secure office at each site. Participants who qualified for the study were assigned the next available randomisation envelope. No envelopes were reused
Blinding (performance bias and detection bias) All outcomes	Low risk	All participants, monitors, site staff and central study staff were unaware of the group assignments. After the DSMB recommended that the trial be stopped, the lead statistician was made aware of the assignments to verify randomisation procedures and interim analyses that had been conducted by an independent statistician. Once these were verified, the lead principal investigator was also made aware of the assignments. All participants, laboratory staff, site investigators and other study staff remained unaware of the assignments until all final follow-up visits and HIV testing were completed
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up comprised 10.7% in the intervention group and 9.0% in the control group 2.4% in the intervention group and 1.0% in the control group discontinued the study prematurely
Selective reporting (reporting bias)	Low risk	The study protocol stated that HIV incidence was the primary outcome, and gonococcal and chlamydial infections the secondary outcomes. Other outcomes re-

		ported included STIs (syphilis, trichomoniasis, Herpes simplex, condyloma acuminatum) and vaginal infections (bacterial vaginosis and yeast)
Other bias	Low risk	Trial stopped early for data-dependent processes, but we do not think that this could have introduced bias to the study

AIDS: acquired immunodeficiency syndrome; ARV: antiretroviral; CAPRISA: Centre for the AIDS Programme of Research in South Africa; CS: cellulose sulphate; DAIDS: Division of AIDS; DNA: deoxyribonucleic acid; DSMB: Data Safety Monitoring Board; ELISA: enzyme-linked immunosorbent assay; FHI: Family Health International; HEC: hydroxyethylcellulose; HIV: human immunodeficiency virus; HR-HPV: high-risk human papillomavirus; HSV: herpes simplex virus; IPM: International Partnership for Microbicides; ITT: intention to treat; NIAID: National Institute of Allergy and Infectious Diseases; ORT: oral mucosal transudate; PCR: polymerase chain reaction; PEPFAR: President's Emergency Plan for AIDS Relief; PMPA: 9-[(*R*)-2-phosphonomethoxy)propyl]adenine monohydrate; RNA: ribonucleic acid; RPR: rapid plasma reagin; SDA: strand displacement amplification; SDMC: Statistical and Data Management Centre; STI: sexually transmitted infections; TPHA: treponema pallidum haemagglutination assay; USAID: United States Agency for International Development.

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

Study	Reason for exclusion
Artz 2005	The microbicide used in the study was Nonoxynol-9 which has already been covered in another Cochrane systematic review (Wilkinson 2002a)
Ettiegne-Traore 1997	The microbicide used in the study was Nonoxynol-9 which has already been covered in another Cochrane systematic review (Wilkinson 2002a)
Lourens 2002	In vitro and animal studies
Rosenberg 1987	The microbicide used in the study was Nonoxynol-9 which has already been covered in another Cochrane systematic review (Wilkinson 2002a)
Straten 2007	The study included HIV positive women

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

NCT00705679

Trial name or title	Safety and effectiveness of tenofovir 1% gel, tenofovir disproxil fumarate, and emtricitabine/tenofovir disoproxil fumerate tablets in preventing HIV in women
Methods	Randomised trial in Malawi, South Africa, Uganda and Zimbabwe
Participants	Healthy non-pregnant sexually active (defined as having vaginal intercourse at least once in the 3 months prior to screening) female volunteers between 18 and 45 years of age with no known adverse reaction to any of the study products or latex. They are willing to provide adequate locator information and agree to use effective method of contraception. Exclusion criteria includes HIV infection, known adverse reaction to any of the study products or latex, pathological bone structure not related to trauma, non-therapeutic injection drug use in the 12 months prior to screening, postexposure prophylaxis for HIV exposure within 6 months prior to enrolment, last pregnancy outcome 42 days or less prior to enrolment, participation in any other research study involving drugs, medical devices or vaginal products 30 days or less prior to enrolment, gynaecological or genital procedure 42 days or less prior to enrolment, currently using spermicide, interferon or interleukin therapy, or certain medications, any significant uncontrolled active or chronic disease, certain abnormal laboratory values, intends to become pregnant in the 24 months after enrolment, plans to relocate or travel away from the study site for more than 8 consecutive weeks in the 24 months after enrolment, having urinary tract infection, pelvic inflammatory diseases, an STI, or reproductive tract infection requiring treatment, grade 2 or higher risk pelvic examination finding, any condition that, in the opinion of the investigator, would interfere with the study, pregnant or breastfeeding
Interventions	INTERVENTION GROUP: tenofovir 1% vaginal gel CONTROL GROUP: tenofovir placebo gel The gels are applied once daily
Outcomes	HIV infection
Starting date	September 2009
Contact information	NIAID
Notes	Sponsors and collaborators: NIAID, Microbicide Trials Network

NCT01386294

Trial name or title	Safety and effectiveness of tenofovir gel in the prevention of HIV-1 infection in young women and the effects of tenofovir gel on the incidence of HSV-2 infection
Methods	Randomised double-blind trial in South Africa
Participants	Non-pregnant, HIV-negative sexually active (defined as having vaginal intercourse at least twice in the past 30 days prior to screening) female volunteers between 16 and 30 years of age. Those able and willing to provide written informed consent, adequate locator information for study retention and safety purposes, and agree to use a study-approved effective non-barrier form of contraception, agree to adhere to study visits and procedures, willing to use study gel as advised, not using or taking any of the following groups of medication; nephrotoxic agents, drugs that slow renal excretion, immune system modulators, or other ARVs. Eligible participant with speculum pelvic examination findings involving deep epithelial disruption may proceed with

NCT01386294 (*Continued*)

	enrolment after the finding resolves. Women currently breastfeeding may be enrolled in the study. Exclusion criteria includes history of adverse reaction to latex, those planning to travel away from the study site for more than 30 consecutive days, relocate away from the study site, become pregnant or enrol in any other study of an investigational product or behaviour modification related to HIV prevention. Those with inadequate renal function (serum creatinine < 1.5 mg/dL and creatinine clearance < 50 mL/minute, as estimated using the method of Cockcroft and Gaulf), abnormal liver phosphate levels (grade 3 and above) and those with clinically apparent finding on speculum pelvic examination (observed by study staff) involving deep epithelial disruption
Interventions	INTERVENTION GROUP: tenofovir gel at concentrations of 1% formulated in purified water with edentate disodium, citric acid, glycerine, methylparaben, propylparaben, HEC and pH adjusted to 4 to 5. Tenofovir gel supplied in a 4-mL single-use applicator containing approximately 4 g of gel equivalent to approximately 40 mg of tenofovir CONTROL GROUP: universal placebo gel. An inert gel containing HEC as the gelling agent, purified water, sodium chloride, sorbic acid and sodium hydroxide. Each applicator contains 4 mL of placebo gel Participants will be required to insert a single dose of assigned gel intravaginally up to 12 hours before each act of vaginal intercourse and a second dose within 12 hours after coitus but not more than 2 applications within a 24-hour period
Outcomes	Incidence of HIV-1 infection determined by using 2 HIV rapid tests. 1 of the rapid tests will detect both HIV-1 and HIV-2; the other will be specific for HIV-1 Safety, grade 2, 3 and 4 clinical and laboratory adverse events as defined by the DAIDS toxicity table HSV-2 status tested by HSV Western blot. Samples positive on HSV Western blot will be deemed to be deemed to be incident HSV-2 infections
Starting date	August 2011
Contact information	CONRAD
Notes	Sponsors and collaborators: CONRAD, FACTS, USAID

ARV: antiretroviral; FACTS: Follow on consortium studies; HEC: hydroxyethylcellulose; HIV: human immunodeficiency virus; HSV: herpes simplex virus; NIAID: National Institute of Allergy and Infectious Diseases; STI: sexually transmitted infections; USAID: United States Agency for International Development.

DATA AND ANALYSES

Comparison 1. Topical microbicide versus placebo - dichotomous data

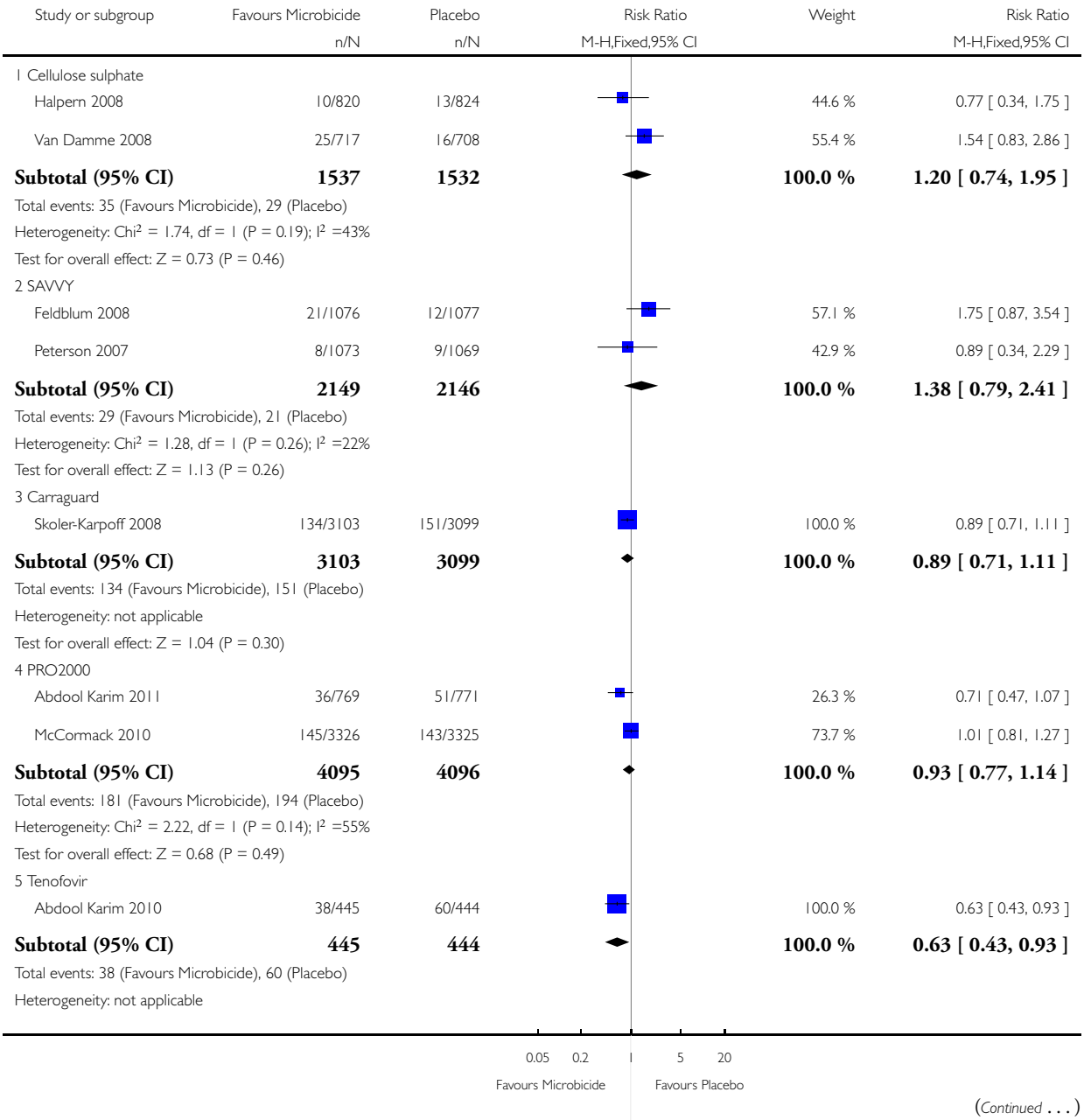
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HIV incidence	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Cellulose sulphate	2	3069	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.74, 1.95]
1.2 SAVVY	2	4295	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.79, 2.41]
1.3 Carraguard	1	6202	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.11]
1.4 PRO2000	2	8191	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.14]
1.5 Tenofovir	1	889	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.43, 0.93]
1.6 BufferGel	1	1546	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.73, 1.52]
2 Herpes simplex	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Cellulose sulphate	1	1425	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.37, 2.62]
2.2 PRO2000	1	6651	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.23]
2.3 Tenofovir	1	426	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.37, 0.83]
3 Gonorrhoea	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Cellulose sulphate	2	3069	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.67, 1.17]
3.2 Carraguard	1	6202	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.88, 1.27]
3.3 PRO2000	1	6651	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.76, 1.43]
4 Chlamydia	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Cellulose sulphate	2	3069	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.49, 0.99]
4.2 Carraguard	1	6202	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.83, 1.12]
4.3 PRO2000	1	6651	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.20]
5 Syphilis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Cellulose sulphate	1	1425	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.26, 1.81]
5.2 Carraguard	1	6202	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.75, 1.52]
6 Condyloma acuminatum	1	1425	Risk Ratio (M-H, Fixed, 95% CI)	3.46 [0.72, 16.58]
6.1 Cellulose sulphate	1	1425	Risk Ratio (M-H, Fixed, 95% CI)	3.46 [0.72, 16.58]
7 Trichomoniasis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Cellulose sulphate	1	1425	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.62, 1.49]
7.2 Carraguard	1	6202	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.01]
8 High-risk HPV	1	1718	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.86, 1.21]

Analysis 1.1. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 1 HIV incidence.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 1 HIV incidence



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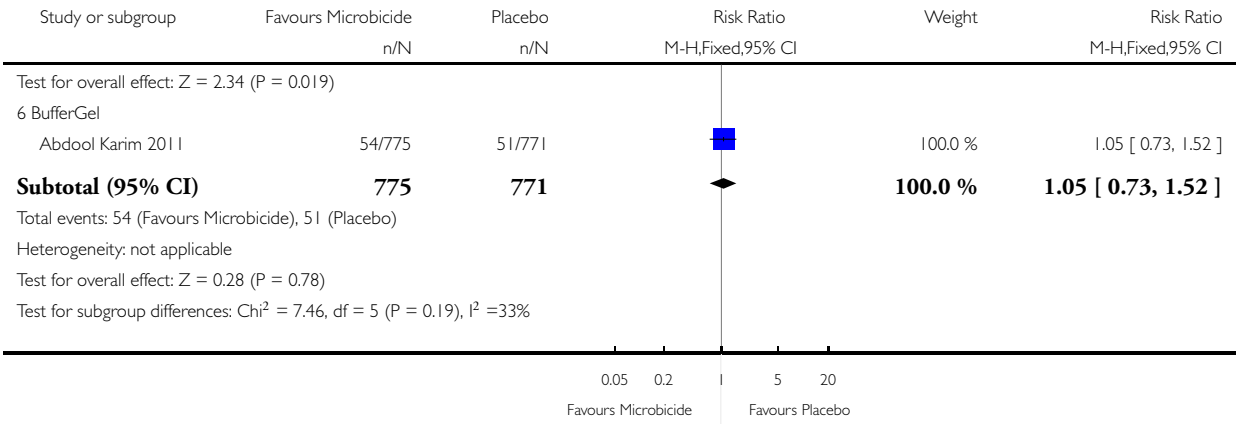
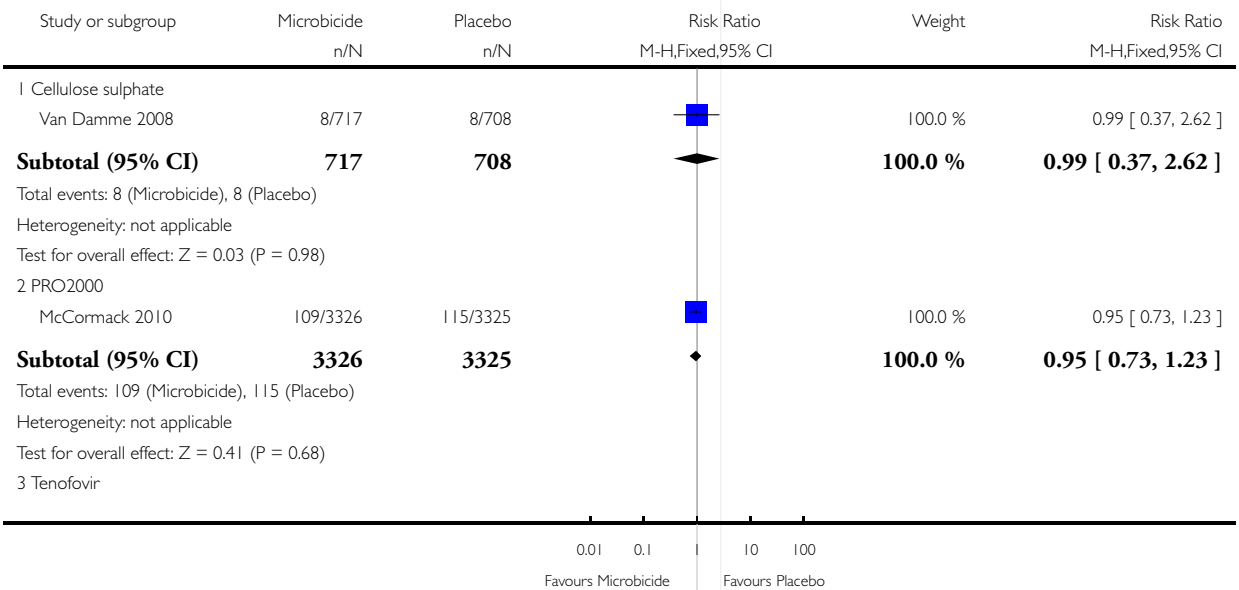


Analysis 1.2. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 2 Herpes simplex.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 2 Herpes simplex



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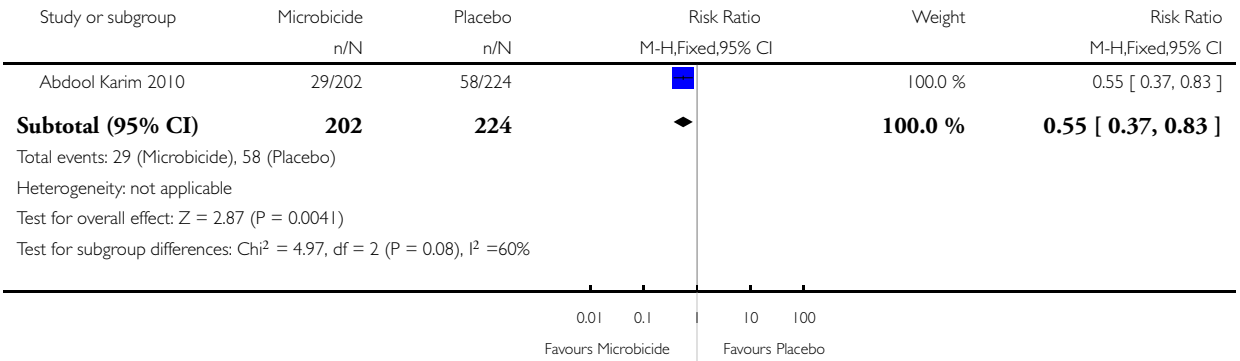
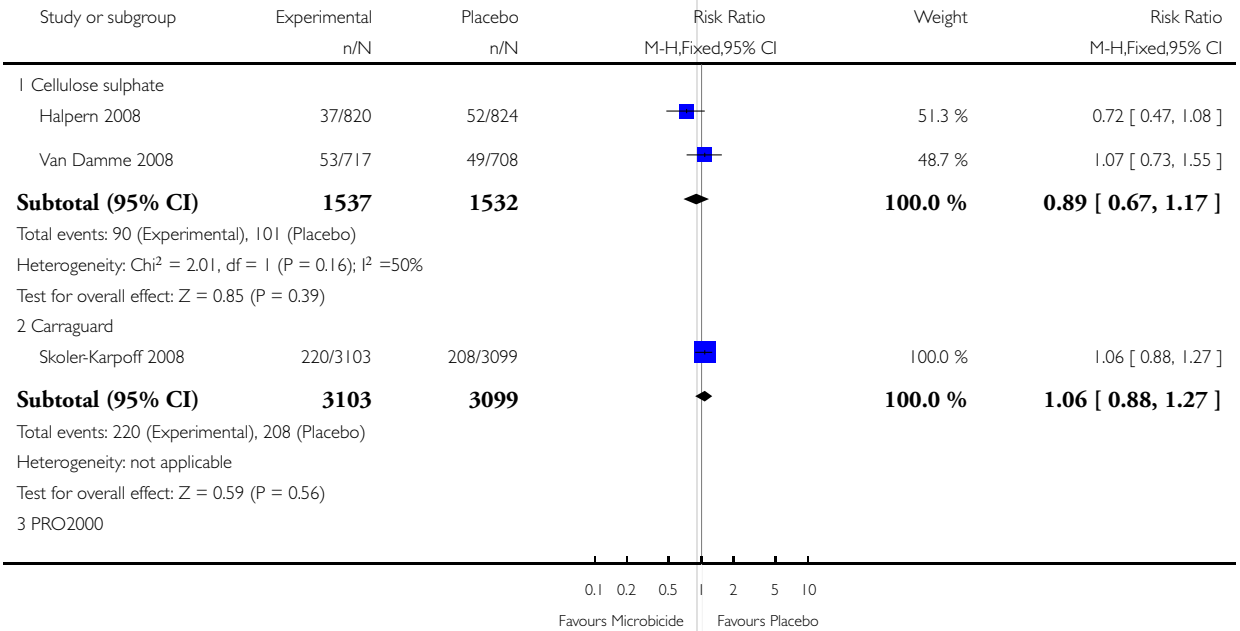


Analysis 1.3. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 3 Gonorrhoea.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 3 Gonorrhoea



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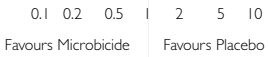
Study or subgroup	Experimental n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McCormack 2010	77/3326	74/3325		100.0 %	1.04 [0.76, 1.43]
Subtotal (95% CI)	**3326**	**3325**		**100.0 %**	**1.04 [0.76, 1.43]**
Total events: 77 (Experimental), 74 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.81)					
Test for subgroup differences: Chi² = 1.12, df = 2 (P = 0.57), I² =0.0%					



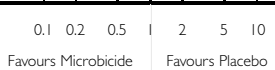
Analysis 1.4. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 4 Chlamydia.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 4 Chlamydia

Study or subgroup	Experimental n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cellulose sulphate					
Halpern 2008	15/820	22/824		29.5 %	0.69 [0.36, 1.31]
Van Damme 2008	37/717	52/708		70.5 %	0.70 [0.47, 1.06]
Subtotal (95% CI)	**1537**	**1532**		**100.0 %**	**0.70 [0.49, 0.99]**
Total events: 52 (Experimental), 74 (Placebo)					
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² =0.0%					
Test for overall effect: Z = 2.04 (P = 0.041)					
2 Carraguard					
Skoler-Karpoff 2008	298/3103	309/3099		100.0 %	0.96 [0.83, 1.12]
Subtotal (95% CI)	**3103**	**3099**		**100.0 %**	**0.96 [0.83, 1.12]**
Total events: 298 (Experimental), 309 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.49 (P = 0.63)					
3 PRO2000					
McCormack 2010	159/3326	164/3325		100.0 %	0.97 [0.78, 1.20]



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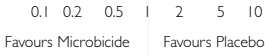
Study or subgroup	Experimental n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**3326**	**3325**		**100.0 %**	**0.97 [0.78, 1.20]**
Total events: 159 (Experimental), 164 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Chi^2 = 3.01, df = 2 (P = 0.22), I^2 =34%					



Analysis 1.5. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 5 Syphilis.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 5 Syphilis

Study or subgroup	Experimental n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cellulose sulphate					
Van Damme 2008	7/717	10/708		100.0 %	0.69 [0.26, 1.81]
Subtotal (95% CI)	**717**	**708**		**100.0 %**	**0.69 [0.26, 1.81]**
Total events: 7 (Experimental), 10 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					
2 Carraguard					
Skoler-Karpoff 2008	63/3103	59/3099		100.0 %	1.07 [0.75, 1.52]
Subtotal (95% CI)	**3103**	**3099**		**100.0 %**	**1.07 [0.75, 1.52]**
Total events: 63 (Experimental), 59 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
Test for subgroup differences: Chi^2 = 0.69, df = 1 (P = 0.41), I^2 =0.0%					

Analysis 1.6. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 6 Condyloma acuminatum.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 6 Condyloma acuminatum

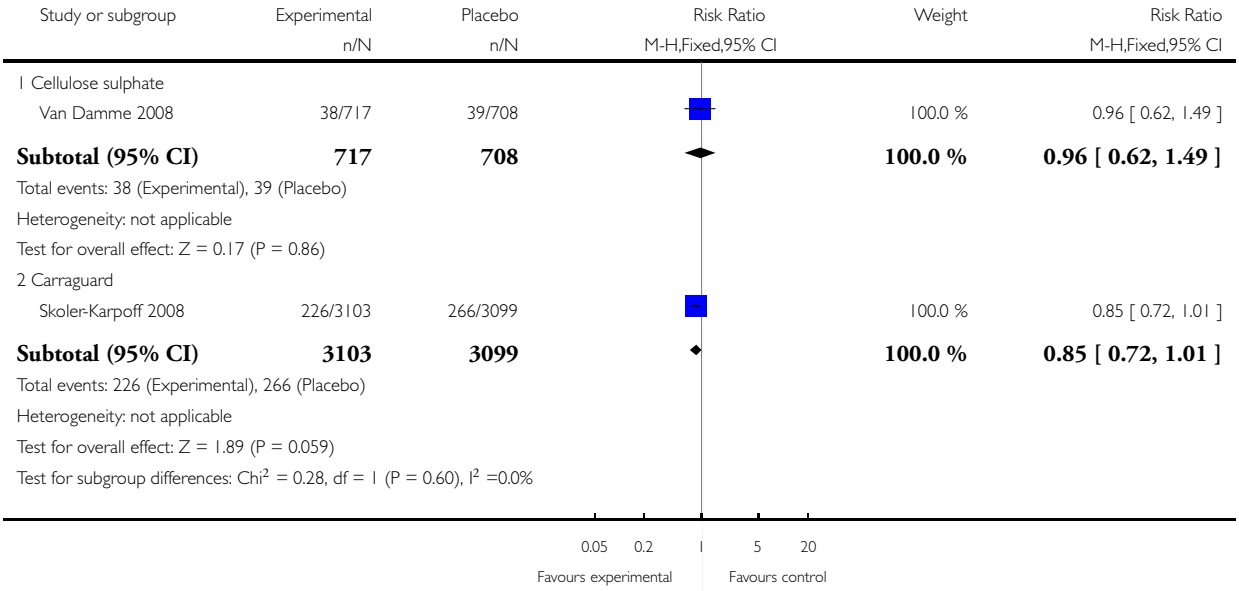
Study or subgroup	Favours experimental n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cellulose sulphate					
Van Damme 2008	7/717	2/708		100.0 %	3.46 [0.72, 16.58]
Total (95% CI)	**717**	**708**		**100.0 %**	**3.46 [0.72, 16.58]**
Total events: 7 (Favours experimental), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
Test for subgroup differences: Not applicable					

Analysis 1.7. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 7 Trichomoniasis.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 7 Trichomoniasis

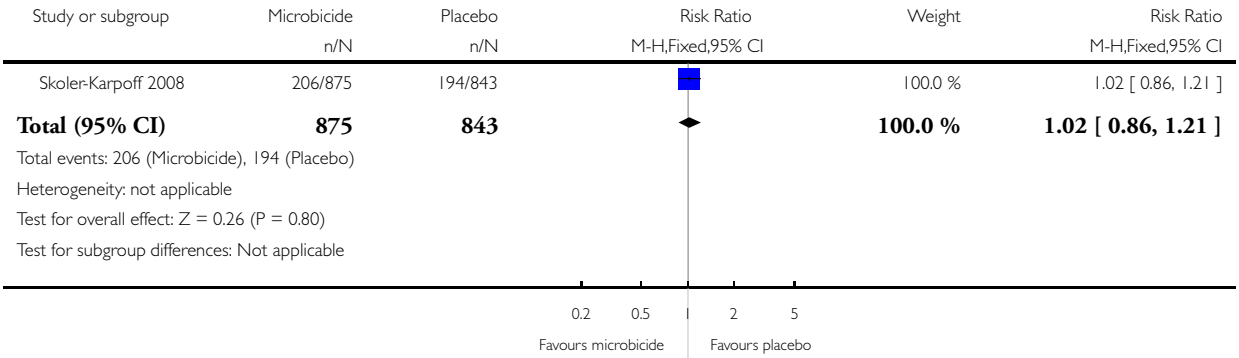


Analysis 1.8. Comparison 1 Topical microbicide versus placebo - dichotomous data, Outcome 8 High-risk HPV.

Review: Topical microbicides for prevention of sexually transmitted infections

Comparison: 1 Topical microbicide versus placebo - dichotomous data

Outcome: 8 High-risk HPV



ADDITIONAL TABLES

Table 1. Search results STD Review Group

Database	Number of articles	Search dates
CENTRAL	252	21 May 2009
Web of Science	10	26 May 2009
MEDLINE/Pubmed	705	17 May 2009
EMBASE	708	26 May 2009
LILACS	45	14 May 2009
NMLGateway	97	18 May 2009
WHOTrial Registry	12	14 May 2009
ClinicalTrials.gov	1508	14 May 2009

Table 2. Search results HIV Review Group 2009

Database	Number of articles	Search dates
CENTRAL	133	4 December 2009
MEDLINE/Pubmed	858	4 December 2009
EMBASE	875	4 December 2009
NLM Gateway	69	4 December 2009
ClinicalTrial.gov	7	4 December 2009

Table 3. Search results HIV Review group 2011

Database	Number of articles	Search dates
Medline/Pubmed	174	22 July 2011
EMBASE	175	22 July 2011
CLIB	42	22 July 2011

Table 4. Adverse events: Feldblum 2008

	Adverse event	microbicide		placebo		RR (95% CI)
		(n/N (%))	Number of events	(n/N (%))	Number of events	
1	Bacterial vaginosis	109/293	112	114/317	117	0.96 [0.71,1.31]
2	Candidiasis	151/293	168	141/317	152	1.07 [0.87, 1.33]
3	Vulvovaginal pruritus	62/293	71	53/317	55	1.27 [0.91, 1.76]
4	Vagina discharge	27/293	288	20/317	21	1.46 [0.84, 2.55]
5	Genita abscess	7/293	7	11/317	11	0.69 [0.27, 1.75]
6	Menstruation irregular	4/293	4	7/317	7	0.62 [0.18, 2.09]
7	Vagina erythrema	6/293	6	3/317	3	2.16 [0.55, 8.57]
8	Vaginal burning sensation	5/293	5	3/317	3	1.80 [0.43, 7.48]

Table 4. Adverse events: Feldblum 2008 (*Continued*)

9	Vulvovaginitis	2/293	2	5/317	5	0.43 [0.08, 2.21]
10	Genital pain	4/293	4	2/317	2	2.16 [0.40, 11.73]
11	Genital rash	4/293	4	2/317	2	2.16 [0.40, 11.73]
12	Menorrhagia	3/293	3	3/317	4	1.08 [0.22, 5.32]
13	Dyspareunia	3/293	3	2/317	2	1.62 [0.27, 9.64]
14	Vaginal haemorrhage	1/293	1	4/317	4	0.27 [0.03, 2.41]
15	Menstrual disorder	0/293	0	3/317	3	0.15 [0.01, 2.98]
16	Genital lesion	0/293	0	2/317	2	0.22 [0.01, 4.49]
17	Vaginal laceration	1/293	1	1/317	1	1.08 [0.07, 17.22]
18	Vaginitis	0/293	0	2/317	2	0.54 [0.05, 5.93]
19	Oedema genital	1/293	1	0/317	0	3.24 [0.13, 79.34]
20	Vaginal lesion	0/293	0	1/317	1	0.36 [0.01, 8.82]
21	Vaginal ulceration	0/293	0	1/317	1	0.36 [0.01, 8.82]

RR: risk ratio; CI: confidence interval; n: number of women with event ; N: number of women analysed

Table 5. Adverse events: Halpern 2008

	Adverse event	microbicide		placebo		RR (95% CI)
		n/N (%)	Number of events	n/N (%)	Number of events	
1	Bacterial vaginosis	74/169	88	77/160	98	0.97 [0.71,1.31]
2	Candidiasis	43/169	52	51/160	65	1.02 [0.70, 1.49]
3	Genital pruritus female	70/169	82	65/160	78	1.02 [0.79,1.32]
4	Menstrual disorder	41/169	51	48/160	56	0.81 [0.57,1.15]
5	Vaginal discharge	31/169	35	38/160	39	0.77 [0.51,1.18]

Table 6. Adverse event: Peterson 2007

Adverse event		Microbicide		Placebo		RR(95%CI)
		n/N	Number of events	n/N	Number of events	
1	Bacterial vaginosis	19/107	19	14/80	16	1.35 [0.68, 2.68]
	Candidiasis	28/107	29	28/80	30	1.00 [0.59, 1.67]
2	Amenorrhoea	3/107	3	0/80	0	5.25 [0.28, 100.22]
3	Cervicitis	0/107	0	1/80	1	0.25 [0.01, 6.06]
4	Dysmenorrhoea	6/107	6	4/80	4	1.12 [0.33, 3.84]
5	Dyspareunia	1/107	1	1/80	1	0.75 [0.05, 11.77]
6	Genital abscess	1/107	1	2/80	2	0.37 [0.03, 4.05]8
7	Genital pruritus female	27/107	28	20/80	23	1.01 [0.61, 1.66]
8	Menorrhagia	1/107	1	2/80	2	0.37 [0.03, 4.05]
9	Menstruation irregular	7/107	7	7/80	6	0.75 [0.27, 2.05]
10	Ovulation pain	1/107	1	1/80	1	0.75 [0.05, 11.77]
11	Pelvic inflammatory diseases	5/107	5	4/80	4	0.93 [0.26, 3.37]
12	Post coital bleeding	1/107	1	1/80	1	0.75 [0.05, 11.77]
13	Vaginal abscess	3/107	3	1/80	1	2.24 [0.24, 21.17]
14	Vaginal burning sensation	0/107	0	3/80	2	0.15 [0.01, 3.08]
15	Vaginal discharge	16/107	16	13/80	14	0.92 [0.47, 1.80]
16	Vaginal erythrema	3/107	4	0/80	0	6.75 [0.37, 123.60]
17	Vaginal haemorrhage	0/107	0	1/80	1	0.25 [0.01, 6.06]

Table 6. Adverse event: Peterson 2007 (*Continued*)

18	Vaginal laceration	0/107	0	2/80	2	0.15 [0.01, 3.08]
19	Vaginal pain	2/107	2	1/80	1	1.50 [0.14, 16.20]
20	Vulvovaginal ulceration	1/107	1	1/80	1	0.75 [0.05, 11.77]
21	Vulvovaginitis	11/107	11	5/80	5	1.64 [0.60, 4.55]

RR: risk ratio; CI: confidence interval; n: number of women with event ; N: number of women analysed

Table 7. Adverse events: Skoler-Karpoff 2008

Adverse event		Microbicide	Placebo	RR(95%CI)
		n/N	N/n	
1	Bacterial vaginosis	266/3103	278/3099	0.96 [0.81, 1.12]
2	Vaginal discharge	162/3103	139/3099	1.16 [0.93, 1.45]
3	Dysmenorrheoa	80/3103	90/3099	0.89 [0.66, 1.19]
4	Genital pruritis	51/3103	51/3099	1.00 [0.68, 1.47]
5	Lower abdominal pain	32/3103	38/3099	0.84 [0.53, 1.34]
6	Disrupted epithelium	105/3103	132/3099	0.79 [0.62, 1.02]
7	Abnormal pap smear	117/3103	135/3099	0.87 [0.68, 1.10]

RR: risk ratio; CI: confidence interval; n: number of women with event ; N: number of women analysed
4 Adverse events

Table 8. Adverse events: Van Damme 2008

Adverse event		Microbicide		Placebo		RR(95%CI)
		n/N	Number of events	n/N	Number of event	
1	Bacterial vaginosis	316/706	496	339/692	542	1.23 [1.13,1.33]
2	Genital infection	316/706	496	77/692	101	0.91 [0.82,1.02]

Table 8. Adverse events: Van Damme 2008 (*Continued*)

3	Cervicitis	39/706	67	52/692	83	0.74 [0.49,1.10]
4	Pelvic inflammatory disease	42/706	49	39/692	49	1.06 [0.69,1.61]
5	Urinary tract infection	39/706	48	40/692	52	0.96 [0.62,1.47]
6	Genital pruritus female	62/706	67	56/692	60	1.09 [0.77,1.53]
7	Metrorrhagia	41/706	46	43/692	46	0.93 [0.62,1.41]
8	Vaginal discharge	41/706	46	30/692	33	1.34 [0.85,2.12]
9	Pelvic pain	17/706	17	15/692	17	1.11 [0.56,2.21]
10	Genital ulceration	10/706	11	8/692	9	1.11 [0.56,2.21]
11	Menorrhagia	8/706	6	10/692	13	0.78 [0.31,1.98]

RR: risk ratio; CI: confidence interval; n: number of women with event ; N: number of women analysed

Table 9. Adverse events: McCormack 2010

	Adverse event	Microbicide		Placebo		RR(95%CI)
		n/N	Number of events	n/N	Number of events	
1	Non menstrual bleeding	551/3326		527/3325		1.05 [0.93, 1.20]
2	Ulcers (Internal)	32/3326		38/3325		0.84 [0.52, 1.35]
3	Ulcers (External)	161/3326		157/3325		1.03 [0.82, 1.29]
4	Oedema (Internal)	11/3326		15/3325		0.73 [0.34, 1.60]
5	Oedema (External)	8/3326		5/3325		1.60 [0.52, 4.90]
6	Erythrema (Internal)	201/3326		201/3325		1.00 [0.82, 1.22]
7	Erythrema (External)	54/3326		35/3325		1.55 [1.01, 2.38]

Table 9. Adverse events: McCormack 2010 (*Continued*)

8	Itching	349/3326		310/3325		1.14 [0.97, 1.34]
9	Burning	72/3326		56/3325		1.29 [0.91, 1.84]
10	Other genital events	379/3326		356/3325		1.07 [0.92, 1.25]
11	Other non genital events	685/3326		631/3325		1.11 [0.98, 1.25]
12	Death	9/3326		5/3325		1.80 [0.60, 5.38]
13	Other serios adverse events	142/3326		119/3325		1.20 [0.94, 1.54]

Table 10. Adverse events: Abdool Karim 2010

	Adverse event	Microbicide		Placebo		RR(95%CI)
		n/N	Number of events	n/N	Number of events	
1	Death	0	0	1/444	1	0.33 [0.01, 8.17]
2	Pregnancy relate SAEs	8/445	8	9/444	8	0.88 [0.34, 2.31]
3	Grade 3 SAEs	15/445	19	16/444	18	0.93 [0.46, 1.91]
4	Grade 4 SAEs	4/445	4	3/444	4	1.33 [0.30, 5.99]
5	Influenza	216/445	365	22/444	314	0.96 [0.74, 1.25]
6	Vaginal discharge	156/445	203	156/444	239	1.00 [0.76, 1.31]
7	Candidiasis	114/445	156	130/444	187	0.83 [0.62, 1.12]
8	Headache	93/445	126	102/444	133	0.89 [0.64, 1.22]
9	UTI	100/445	135	93/444	120	1.09 [0.80, 1.51]
10	Diarrhea and GTIs	75/445	91	49/444	65	1.63 [1.11, 2.41]
11	Upper respitatory tract infections	114/445	162	100/444	145	1.18 [0.87, 1.61]
12	Disrupted epithelim (e.g. genital ulceration)	18/445	18	13/444	14	1.40 [0.68, 2.89]

Table 10. Adverse events: Abdool Karim 2010 (*Continued*)

13	Intact epithelium (e.g.erythrema)	41/445	48	33/444	42	1.27 [0.79, 2.04]
14	Urogenital symptoms (e.g. menorrhagia)	210/445	312	238/444	394	0.48 [0.37, 0.63]
15	AST	21/445	29	29/444	36	0.71 [0.40, 1.26]
16	ALT	33/445	42	40/444	50	0.81 [0.50, 1.31]
17	Raised creatinine	4/445	4	1/444	1	4.02 [0.45, 36.09]
18	Low potassium	95/445	119	83/444	99	1.16 [0.84, 1.62]
19	Raised sodium	48/445	54	41/444	43	1.19 [0.77, 1.84]
20	Anaemia	34/445	52	29/444	46	1.18 [0.71, 1.98]
21	Neutropenia	16/445	19	11/444	13	1.47 [0.67, 3.20]
22	Low phosphate	62/445	79	51/444	65	Not estimable
23	Low calcium	15 /445	16	13/444	14	1.16 [0.54, 2.46]

Table 11. Abdool Karim 2011 PRO2000

	Adverse event		Microbicide	Placebo		RR(95%CI)
		n/N	Number of events	n/N	Number of events	
1	Deaths	2/769		1/771		2.01 [0.18, 22.19]
2	Hospitalization	30/769		30/771		1.00 [0.60, 1.68]
3	Reproductive system events	393/769		387/771		1.04 [0.85, 1.27]
4	Vaginal discharge	221/769		202/771		1.14 [0.91, 1.42]
5	Vulvovaginal pruritis	97/769		105/771		0.92 [0.68, 1.23]
6	Metrorrgia	55/769		36/771		1.57 [1.02, 2.42]
7	Cervix hemorrhage uterine	36/769		36/771		1.00 [0.62, 1.61]

Table 11. Abdool Karim 2011 PRO2000 (*Continued*)

8	Menorrhagia	31/769		29/771		1.07 [0.64, 1.80]
	Adverse events categories					
9	Genital infection events	577/769		557/771		1.15 [0.92, 1.45]
10	Genital irritation events	308/769		302/771		1.04 [0.85, 1.27]
11	Genital bleeding abnormality events	135/769		116/771		1.20 [0.92, 1.58]
12	Urinary tract events	132/769		109/771		1.26 [0.95, 1.66]
13	Genital pain events	78/769		73/771		1.08 [0.77, 1.51]
14	Genital lesion events	63/769		57/771		1.12 [0.77, 1.62]
15	Intermenstrual bleeding events	63/769		39/771		1.67 [1.11, 2.53]
16	Pregnancy related events	39/769		30/771		1.32 [0.81, 2.15]
17	Coagulation abnormalities	4/769		2/771		2.01 [0.37, 11.01]
18	Systemic liver, renal a coagulation abnormalities during phase II	2/769		1/771		2.01 [0.18, 22.19]
19	Pelvic examination finding (events per 100 person-years)					0.99 [0.06, 15.93]
20	Deep epithelial disruption	1.7		1.5		
21	Abnormal vaginal discharge	78.2		73.7		
22	Any blood related finding	16.1		15.3		

Table 11. Abdool Karim 2011 PRO2000 (*Continued*)

23	Blood from cervical os	9.8		10.5		
24	Erythrema	7.9		7.4		
25	Petechia	3.9		4.6		
26	Blood-tinged discharge	2.4		2.6		
27	Blood in vagina, no identified source	3.5		1.8		
28	Ulceration	1.9		1.9		

Table 12. Abdool Karim 2011 BufferGel

	Adverse event	Microbicide		Placebo		RR(95%CI)
		n/N	Number of events	n/N	Number of events	
1	Deaths	2/775		1/771		1.99 [0.18, 22.02]
2	Hospitalization	37/775		30/771		1.24 [0.76, 2.03]
3	Reproductive system events	412/775		387/771		1.13 [0.92, 1.37]
4	Vaginal discharge	229/775		202/771		1.18 [0.95, 1.48]
5	Vulvovaginal pruritis	115/775		105/771		1.11 [0.83, 1.47]
6	Metrorrgia	53/775		36/771		1.50 [0.97, 2.32]
7	Cervix hemorrhage uterine	39/775		36/771		1.08 [0.68, 1.72]
8	Menorrhagia	34/775		29/771		1.17 [0.71, 1.95]
	Adverse events categories					
9	Genital infection events	563/775		577/771		0.89 [0.71, 1.12]
10	Genital irritation events	317/775		302/771		1.07 [0.88, 1.32]

Table 12. Abdool Karim 2011 BufferGel (*Continued*)

11	Genital bleeding abnormality events	140/775		116/771		1.24 [0.95, 1.63]
12	Urinary tract events	126/775		109/771		1.18 [0.89, 1.56]
13	Genital pain events	79/775		73/771		1.09 [0.78, 1.52]
14	Genital lesion events	78/775		57/771		1.40 [0.98, 2.00]
15	Intermenstrual bleeding events	56/775		39/771		1.46 [0.96, 2.23]
16	Pregnancy related events	41/775		30/771		1.38 [0.85, 2.23]
17	Coagulation abnormalities	2/775		2/771		0.99 [0.14, 7.08]
18	Systemic liver, renal a coagulation abnormalities during phase II	1/775		1/771		
19	Pelvic examination finding (events per 100 person-years)					
20	Deep epithelial disruption	1.7		1.5		
21	Abnormal vaginal discharge	77.4		73.7		
22	Any blood related finding	17.4		15.3		
23	Blood from cervical os	10.7		10.5		
24	Erythrema	6.3		7.4		
25	Petechia	5.0		4.6		
26	Blood-tinged discharge	4.0		2.6		

Table 12. Abdool Karim 2011 BufferGel (*Continued*)

27	Blood in vagina, no identified source	2.5		1.8		
28	Ulceration	2.6		1.9		

APPENDICES

Appendix 1. Search strings, STD review group

Table 1. (Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science)

Search set	CENTRAL	Web of Science
1	microbicid*:ti,ab,kw OR spermicid*:ti,ab,kw	TS=(microbicid* OR spermicid*)
2	(topical:ti,ab,kw OR vaginal:ti,ab,kw OR rectal:ti,ab,kw) AND (microbicid*:ti,ab,kw OR spermicid*:ti,ab,kw)	TS=((topical OR vaginal OR rectal) AND microbicid*)
3	(antimicrobial:ti,ab,kw) AND (vaginal:ti,ab,kw OR rectal: ti,ab,kw	TS=((vaginal OR rectal OR topical) AND antimicrobial)
4	4 #1 OR #2 OR #3, from 1980 to 2009	#1 OR #2 OR #3
5		TS=(sexually transmitted disease* OR sexually transmissible disease* OR sexually transmitted infection* OR sexually transmissible infection* OR sexually transmitted infectious disease* OR sexually transmissible infectious disease* OR sexually transmitted disorder* OR sexually transmissible disorder* OR STI OR STD OR genital ulcer* OR genital ulcer disease* OR genital infection* OR genital disorder* OR venereal disease* OR venereal infection* OR venereal disorder*)
6		TS=(herpes genitalis OR genital herpes OR herpes virus OR HSV-1 OR HSV-2 OR gonorrhea OR neisseria gonorrhoeae OR gonococcal urethritis OR syphilis OR treponema pallidum OR chancre OR primary syphilis OR secondary syphilis OR condylomata lata OR candida albicans OR monilia albicans OR candidiasis OR candidal vaginitis OR candidosis OR vulvovaginitis OR vulvitis OR vulvovaginal candidiasis OR vulvodynia OR balanitis OR lym-

(*Continued*)

		phogranuloma venereum OR chlamydia trachomatis OR LGV OR human papillomavirus OR cervical cancer OR HPV OR genital wart* OR anogenital wart* OR anorectal wart* OR anorectal wart* OR penile wart* OR condylomata acuminata OR condyloma OR bacterial vaginosis OR gardnerella vaginalis OR bacterial vaginitis OR vaginitis OR vaginosis)
7		#5 OR #6
8		TS=((randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups) AND (humans)
9		#4 AND #7 AND #8

Table 2. (MEDLINE/PubM ed, EMBASE)

Search set	MEDLINE/PubM ed	EMBASE
1	((microbicid*[tiab] OR spermicid*[tiab]) OR ((topical[tiab]) OR (vaginal[tiab]) OR (rectal[tiab]) AND (microbicid*[tiab])) OR ((antimicrobial[tiab]) AND (vaginal[tiab]) OR (rectal[tiab]))) AND (("Sexually Transmitted Diseases"[Mesh] OR "Sexually Transmitted Diseases, Bacterial"[Mesh] OR "Sexually Transmitted Diseases, Viral"[Mesh]) OR (sexually transmitted disease*[tiab] OR sexually transmissible disease*[tiab] OR sexually transmitted infection*[tiab] OR sexually transmissible infection*[tiab] OR sexually transmitted infectious disease*[tiab] OR sexually transmissible infectious disease*[tiab] OR sexually transmitted disorder*[tiab] OR sexually transmissible disorder*[tiab] OR STI[tiab] OR STD[tiab] OR genital ulcer*[tiab] OR genital ulcer disease*[tiab] OR genital infection*[tiab] OR genital disorder*[tiab] OR venereal disease*[tiab] OR venereal infection*[tiab] OR venereal disorder*[tiab]) OR ((sexually transmitted disease*[tiab]) AND (viral[tiab] OR bacterial[tiab] OR fungal[tiab] OR protozoan[tiab])) OR ("Herpes Simplex"[Mesh] OR "Herpes Genitalis"[Mesh] OR herpes simplex[tiab] OR herpes genitalis[tiab] OR genital herpes[tiab] OR herpes virus[tiab] OR HSV-1[tiab] OR HSV-2[tiab]) OR ("Gonorrhea"[Mesh] OR gonorrhea[tiab] OR neisseria gonorrhoeae[tiab] OR gonococcal urethritis[tiab] OR gonococcal urethritis[tiab] OR gono-	((microbicid*:ti OR microbicid*) OR (spermicid*:ti OR spermicid*) OR ((topical:ti OR 'topical'/exp) OR (vaginal:ti OR vaginal) OR (rectal:ti OR 'rectal'/exp) AND (microbicid*:ti OR microbicid*)) OR ((antimicrobial:ti OR 'antimicrobial'/exp) AND (vaginal:ti OR vaginal) OR (rectal:ti OR 'rectal'/exp))) AND [embase]/lim AND [embase]/lim AND [1980-2009]/py

(*Continued*)

	cocci[tiab]) OR ("Syphilis"[Mesh] OR syphilis[tiab] OR treponema pallidum[tiab] OR chancre[tiab] OR primary syphilis[tiab] OR secondary syphilis[tiab] OR condylomata lata[tiab]) OR ("Candida albicans"[Mesh] OR candida albicans[tiab] OR monilia albicans[tiab] OR monilial infection[tiab] OR candidiasis[tiab] OR candida[tiab] OR candidal vaginitis[tiab] OR candidosis[tiab] OR vulvovaginitis[tiab] OR vulvitis[tiab] OR vulvovaginal candidiasis[tiab] OR vulvodynia[tiab] OR balanitis[tiab]) OR ("Chlamydia trachomatis"[Mesh] OR "Lymphogranuloma Venereum"[Mesh] OR lymphogranuloma venereum[tiab] OR chlamydia trachomatis[tiab] OR chlamydia infections[tiab] OR LGV[tiab]) OR ("Human papillomavirus 6"[Mesh] OR "Human papillomavirus 18"[Mesh] OR "Human papillomavirus 11"[Mesh] OR "Human papillomavirus 16"[Mesh] OR "Papillomavirus Infections"[Mesh] OR human papillomavirus[tiab] OR cervical cancer[tiab] OR HPV[tiab] OR genital wart*[tiab] OR anogenital wart*[tiab] OR anorectal wart*[tiab] OR anorectal wart*[tiab] OR penile wart*[tiab] OR condylomata acuminata[tiab] OR condyloma[tiab]) OR ("Vaginosis, Bacterial"[Mesh] OR "Gardnerella"[Mesh] OR "Gardnerella vaginalis"[Mesh] OR "Mobiluncus"[Mesh] OR bacterial vaginosis[tiab] OR gardnerella vaginalis[tiab] OR bacterial vaginitis[tiab] OR vaginitis[tiab] OR vaginosis[tiab])) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) AND (humans[mh]))[TRG1]	
2		('sexually transmitted diseases'/exp OR 'sexually transmitted diseases, bacterial'/exp OR 'sexually transmitted diseases, viral'/exp) OR ((sexually AND transmitted AND disease*:ti OR sexually AND transmitted AND disease*:ab) OR (sexually AND transmissible AND disease*:ti OR sexually AND transmissible AND disease*:ab) OR (sexually AND transmitted AND infection*:ti OR sexually AND transmitted AND infection*:ab) OR (sexually AND transmissible AND infection*:ti OR sexually AND transmissible AND infection*:ab) OR (sexually AND transmitted AND infectious AND disease*:ti OR sexually AND transmitted AND infectious AND disease*:ab) OR (sexually AND transmissible AND infectious AND disease*:ti OR sexually AND transmissible AND infectious AND disease*:ab) OR (sexually AND transmitted AND disorder*:ti OR sexually AND transmitted AND disorder*:ab) OR (sexually AND transmissible AND disorder*:ti OR sexually AND transmissible AND disorder*:ab) OR (sti:ti OR

(*Continued*)

		sti:ab) OR (std:ti OR std:ab) OR (genital AND ulcer*:ti OR genital AND ulcer*:ab) OR (genital AND 'ulcer'/exp AND disease*:ti OR genital AND 'ulcer'/exp AND disease*:ab) OR (genital AND infection*:ti OR genital AND infection*:ab) OR (genital AND disorder*:ti OR genital AND disorder*:ab) OR (venereal AND disease*:ti OR venereal AND disease*:ab) OR (venereal AND infection*:ti OR venereal AND infection*:ab) OR (venereal AND disorder*:ti OR venereal AND disorder*:ab)) OR (((sexually AND transmitted AND disease*:ti OR sexually AND transmitted AND disease*:ab) AND (viral:ti OR viral:ab) OR (bacterial:ti OR bacterial:ab) OR (fungal:ti OR fungal:ab) OR (protozoan:ti OR protozoan:ab))) OR (('herpes simplex'/exp OR 'herpes genitalis'/exp) OR ('herpes'/exp AND simplex:ti OR 'herpes'/exp AND simplex:ab) OR ('herpes'/exp AND genitalis:ti OR 'herpes'/exp AND genitalis:ab) OR (genital AND herpes:ti OR genital AND herpes:ab) OR ('herpes'/exp AND virus:ti OR 'herpes'/exp AND virus:ab) OR ('hsv 1':ti OR 'hsv 1':ab) OR ('hsv 2':ti OR 'hsv 2':ab)) OR (('gonorrhea'/exp) OR (gonorrhea:ti OR gonorrhea:ab) OR ('neisseria'/exp AND gonorrhoeae:ti OR 'neisseria'/exp AND gonorrhoeae:ab) OR (gonococcal AND urethritis:ti OR gonococcal AND urethritis:ab) OR (gonococcal AND urethritis:ti OR gonococcal AND urethritis:ab) OR (gonococci:ti OR gonococci:ab)) OR (('syphilis'/exp) OR (syphilis:ti OR syphilis:ab) OR ('treponema'/exp AND pallidum:ti OR 'treponema'/exp AND pallidum:ab) OR (chancre:ti OR chancre:ab) OR (primary AND syphilis:ti OR primary AND syphilis:ab) OR (secondary AND syphilis:ti OR secondary AND syphilis:ab) OR ('condylomata'/exp AND lata:ti OR 'condylomata'/exp AND lata:ab)) OR (('candida albicans'/exp) OR ('candida'/exp AND albicans:ti OR 'candida'/exp AND albicans:ab) OR ('monilia'/exp AND albicans:ti OR 'monilia'/exp AND albicans:ab) OR (monilial AND infection:ti OR monilial AND infection:ab) OR (candidiasis:ti OR monilial AND infection:ab) OR (candida:ti OR candida:ab) OR (candidal AND vaginitis:ti OR candida:ab) OR (candidosis:ti OR candidosis:ab) OR (vulvovaginitis:ti OR vulvovaginitis:ab) OR (vulvitis:ti OR vulvitis:ab) OR (vulvovaginal AND candidiasis:ti OR vulvovaginal AND candidiasis:ab) OR (vulvodynia:ti OR vulvodynia:ab) OR (balanitis:ti OR balanitis:ab)) OR (('chlamydia trachomatis'/exp) OR ('lymphogranuloma venereum'/exp) OR (lymphogranuloma AND venereum:ti OR lymphogranuloma AND venereum:ab) OR ('chlamydia'/exp AND trachomatis:ti OR 'chlamydia'/exp AND trachomatis:ab) OR ('chlamydia'/exp AND infections:ti OR 'chlamydia'/exp AND in-

(*Continued*)

		fections:ab) OR (lgv:ti OR lgv:ab)) OR (('human papillomavirus 6'/exp) OR ('human papillomavirus 18'/exp) OR ('human papillomavirus 11'/exp) OR ('human papillomavirus 16'/exp) OR ('papillomavirus infections'/exp) OR ('human'/exp AND papillomavirus:ti OR 'human'/exp AND papillomavirus:ab) OR (cervical AND cancer:ti OR cervical AND cancer:ab) OR (hpv:ti OR hpv:ab) OR (genital AND wart*:ti OR genital AND wart*:ab) OR (anogenital AND wart*:ti OR anogenital AND wart*:ab) OR (anorectal AND wart*:ti OR anorectal AND wart*:ab) OR (anorectal AND wart*:ti OR anorectal AND wart*:ab) OR (penile AND wart*:ti OR penile AND wart*:ab) OR ('condylomata'/exp AND acuminata:ti OR 'condylomata'/exp AND acuminata:ab) OR (condyloma:ti OR condyloma:ab)) OR (('vaginosis, bacterial'/exp) OR ('gardnerella'/exp) OR ('gardnerella vaginalis'/exp) OR ('mobiluncus'/exp) OR (bacterial AND vaginosis:ti OR bacterial AND vaginosis:ab) OR ('gardnerella'/exp AND vaginalis:ti OR 'gardnerella'/exp AND vaginalis:ab) OR (bacterial AND vaginitis:ti OR bacterial AND vaginitis:ab) OR (vaginitis:ti OR vaginitis:ab) OR (vaginosis:ti OR vaginosis:ab)) AND [embase]/lim AND [1980-2009]/py
3		(random*:ti OR random*:ab) OR (factorial*:ti OR factorial*:ab) OR (cross?over*:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab) OR (placebo*:ti OR placebo*:ab) OR (((doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab))) OR (((singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab))) OR (assign*:ti OR assign*:ab) OR (volunteer*:ti OR volunteer*:ab) OR ((((('crossover procedure'/exp OR 'crossover procedure'/exp) OR ('crossover procedure'/exp OR 'crossover procedure'/exp)) OR (('crossover procedure'/exp OR 'crossover procedure'/exp) OR ('crossover procedure'/exp OR 'crossover procedure'/exp))) OR ((('crossover procedure'/exp OR 'crossover procedure'/exp) OR ('crossover procedure'/exp OR 'crossover procedure'/exp)) OR (('crossover procedure'/exp OR 'crossover procedure'/exp) OR ('crossover procedure'/exp OR 'crossoverprocedure'))))) OR (((((('double-blind procedure'/exp OR 'double-blind procedure'/exp) OR ('double-blind procedure'/exp OR 'double-blind procedure'/exp)) OR (('double-blind procedure'/exp OR 'double-blind procedure'/exp) OR ('double-blind procedure'/exp OR 'double-blind procedure'/exp))) OR ((('double-blind procedure'/exp OR 'double-blind procedure'/exp) OR ('double-blind procedure'/exp OR 'double-blind procedure'/exp)) OR (('double-blind procedure'/exp OR 'double-blind procedure'/exp) OR ('double-blind procedure'/exp OR 'double-blind procedure'/exp))))) OR (((((sin-

(*Continued*)

		gle-blind procedure'/exp OR 'single-blind procedure'/exp) OR ('single-blind procedure'/exp OR 'single-blind procedure'/exp)) OR (('single-blind procedure'/exp OR 'single-blind procedure'/exp) OR ('single-blind procedure'/exp OR 'single-blind procedure'/exp))) OR ((('single-blind procedure'/exp OR 'single-blind procedure'/exp) OR ('single-blind procedure'/exp OR 'single-blind procedure'/exp)) OR (('single-blind procedure'/exp OR 'single-blind procedure'/exp) OR ('single-blind procedure'/exp OR 'single-blind procedure'/exp))))) OR (((((('randomized controlled trial'/exp OR 'randomized controlled trial'/exp) OR ('randomized controlled trial'/exp OR 'randomized controlled trial'/exp)) OR (('randomized controlled trial'/exp OR 'randomized controlled trial'/exp) OR ('randomized controlled trial'/exp OR 'randomized controlled trial'/exp))) OR ((('randomized controlled trial'/exp OR 'randomized controlled trial'/exp) OR ('randomized controlled trial'/exp OR 'randomized controlled trial'/exp)) OR (('random- ized controlled trial' OR 'randomized controlled trial'/exp) OR ('randomized controlled trial'/exp OR 'randomized controlled trial'/exp))))) OR (allocat*:ti OR allocat*:ab) AND [embase]/lim AND [embase]/lim AND [1980-2009]/py
4		#1 AND #2 AND #3

Table 3. (LILACS, NLM Gateway, WHO ICTRP, ClinicalTrials.gov)

Search set	LILACS	NLM Gateway	WHO ICTRP	ClinicalTrials.gov
1	microbicid$ OR spermicid$ OR (topical OR vaginal OR rectal) AND (microbicid$) OR (antimicrobial) AND (vaginal OR rectal) [Palavras do resumo] or microbicid$ OR spermicid$ OR (topical OR vaginal OR rectal) AND (microbicid$) OR (antimicrobial) AND (vaginal OR rectal) [Palavras do título] and ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled tri-	antimicrobial OR microbicide OR microbicides OR microbicidal OR spermicide OR spermicides OR spermicidal AND sexually transmitted disease	(antimicrobial OR microbicid* OR spermicid*) on Title and Intervention for ALL recruiting status	antimicrobial OR microbicide OR microbicides OR microbicidal OR spermicide OR spermicides OR spermicidal | Sexually Transmitted Infections

(*Continued*)

	als OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Palavras]			

[TRG1] I used the Cochrane Highly Sensitive Search Strategy for identifying randomis ed trials in MEDLINE: sensitivity-maximis ing version (2008 revision); PubMed format.

Appendix 2. Search strings, HIV Review Group 2009

Table 4. (Cochrane Central Register of Controlled Trials (CENTRAL), Gateway)

Search set	CENTRAL	Hits	Gateway	Items Found
#1	MeSH descriptor HIVexplode all trees	1828	Search: (((HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNODEFI- CIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME))) OR (((ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)))	379551
#2	MeSH descriptor HIV Infections explode all trees	5850	Search: (SEXUALLY TRANSMITTED INFECTION OR SEXUALLY TRANSMITTED INFECTIONS) OR (SEXUALLY TRANSMITTED DISEASE OR SEXUALLY TRANSMITTED DISEASES)	261963
#3	(#1 OR #2)	5936	Search: MICROBICIDE OR MICROBICIDES OR SPERMICIDE OR SPERMICIDES OR MICROBICIDAL OR SPERMICIDAL OR ANTIMICROBIAL	1102789
#4	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNED-	8658	Search: RANDOMIZED CONTROLLED TRIAL OR CONTROLLED CLINICAL TRIAL OR RANDOMIZED OR PLACEBO OR DRUG THERAPY OR RANDOMLY OR TRIAL OR GROUPS	3529526

(*Continued*)

	EFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFI- CIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME			
#5	MeSH descriptor Lymphoma, AIDS-Related, this term only	21	Search: ((((HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFI- CIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME))) OR (((ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)))) AND ((SEXUALLY TRANSMITTED INFEC-	35779

(*Continued*)

			TION OR SEXUALLY TRANSMITTED INFECTIONS) OR (SEXUALLY TRANSMITTED DISEASE OR SEXUALLY TRANSMITTED DISEASES)) AND (MICROBICIDE OR MICROBICIDES OR SPERMICIDE OR SPERMICIDES OR MICROBICIDAL OR SPERMICIDAL OR ANTIMICROBIAL) AND (RANDOMIZED CONTROLLED TRIAL OR CONTROLLED CLINICAL TRIAL OR RANDOMIZED OR PLACEBO OR DRUG THERAPY OR RANDOMLY OR TRIAL OR GROUPS) Limit: 1980/01/01: 2009/12/04	
#6	(#3 OR #4 OR #5)	8781		
#7	MeSH descriptor Sexually Transmitted Diseases explode all trees	6922		
#8	sexually transmitted disease*:ti,ab,kw OR sexually transmissible disease*:ti,ab,kw OR sexually transmitted infection*:ti,ab,kw OR sexually transmissible infection*:ti,ab,kw OR sexually transmitted infectious disease*:ti,ab,kw OR sexually transmissible infectious disease*:ti,ab,kw OR sexually transmitted disorder*:ti,ab,kw OR sexually transmissible disorder*:ti,ab,kw OR STI:ti,ab,kw OR STD:ti,ab,kw OR genital ulcer*:ti,ab,kw OR genital ulcer disease*:ti,ab,kw OR genital infection*:ti,ab,kw OR genital disorder*:ti,ab,kw OR venereal disease*:ti,ab,kw OR venereal infection*:ti,ab,kw OR venereal disorder*:ti,ab,kw	2240		

(*Continued*)

#9	(sexually transmitted disease*:ti,ab,kw) AND (viral:ti,ab,kw OR bacterial:ti,ab,kw OR fungal:ti,ab,kw OR protozoan:ti,ab,kw)	154		
#10	herpes simplex:ti,ab,kw OR herpes genitalis:ti,ab,kw OR genital herpes:ti,ab,kw OR herpes virus:ti,ab,kw OR HSV-1:ti,ab,kw OR HSV-2:ti,ab,kw	1074		
#11	gonorrhea:ti,ab,kw OR neisseria gonorrhoeae:ti,ab,kw OR gonococcal urethritis:ti,ab,kw OR gonococcal urethritis:ti,ab,kw OR gonococci:ti,ab,kw	961		
#12	syphilis:ti,ab,kw OR treponema pallidum:ti,ab,kw OR chancre:ti,ab,kw OR primary syphilis:ti,ab,kw OR secondary syphilis:ti,ab,kw OR condylomata lata:ti,ab,kw	270		
#13	candida albicans:ti,ab,kw OR monilia albicans:ti,ab,kw OR monilial infection:ti,ab,kw OR candidiasis:ti,ab,kw OR candida:ti,ab,kw OR candidal vaginitis:ti,ab,kw OR candidosis:ti,ab,kw OR vulvovaginitis:ti,ab,kw OR vulvitis:ti,ab,kw OR vulvovaginal candidiasis:ti,ab,kw OR vulvodynia:ti,ab,kw OR balanitis:ti,ab,kw	1693		
#14	lymphogranuloma venereum:ti,ab,kw OR chlamydia trachomatis:ti,ab,kw OR chlamydia infections:ti,ab,kw OR LGV:ti,ab,kw	898		

(*Continued*)

#15	human papillomavirus:ti,ab,kw OR cervical cancer:ti,ab,kw OR HPV:ti,ab,kw OR genital wart*:ti,ab,kw OR anogenital wart*:ti,ab,kw OR anorectal wart*:ti,ab,kw OR anorectal wart*:ti,ab,kw OR penile wart*:ti,ab,kw OR condylomata acuminata:ti,ab,kw OR condyloma:ti,ab,kw	1896		
#16	bacterial vaginosis:ti,ab,kw OR gardnerella vaginallis:ti,ab,kw OR bacterial vaginitis:ti,ab,kw OR vaginitis:ti,ab,kw OR vaginosis:ti,ab,kw	763		
#17	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	13,089		
#18	MeSH descriptor Herpes Genitalis, this term only	281		
#19	MeSH descriptor Gonorrhea explode all trees	394		
#20	MeSH descriptor Candida albicans, this term only	145		
#21	MeSH descriptor Chlamydia trachomatis, this term only	321		
#22	MeSH descriptor Lymphogranuloma Venereum explode all trees	6		
#23	MeSH descriptor Papillomavirus Infections explode all trees	609		
#24	MeSH descriptor Human papillomavirus 16, this term only	33		

(*Continued*)

#25	MeSH descriptor Vaginosis, Bacterial explode all trees	185		
#26	MeSH descriptor Gardnerella explode all trees	39		
#27	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR # 24 OR #25 OR #26)	1892		
#28	(#17 OR #27)	13,203		
#29	microbicid*:ti,ab,kw OR spermicid*:ti,ab,kw	193		
#30	(topical:ti,ab,kw OR vaginal:ti,ab,kw OR rectal:ti,ab,kw) AND (microbicid*:ti,ab,kw OR spermicid*:ti,ab,kw)	129		
#31	(antimicrobial:ti,ab,kw) AND (vaginal:ti,ab,kw OR rectal:ti,ab,kw)	94		
#32	(#29 OR #30 OR #31)	284		
#33	(#6 OR #28)	16,097		
#34	(#32 AND #33)	143		
#35	(#32 AND #33), from 1980 to 2009	143		

Table 5. (PubMed, EMBASE)

Search set	PubMed	Time	Result	EMBASE	Results	Date
#1	Search (("Sexually Transmitted Diseases"[Mesh] OR "Sexually Transmitted Diseases, Bacterial"[Mesh] OR "Sexually Transmitted Diseases,	05:01:07	365,430	'sexually transmitted diseases'/exp OR 'sexually transmitted diseases, bacterial'/exp OR 'sexually transmitted diseases, viral'/exp OR (sexually AND transmitted AND	761226	4 Dec 2009

(*Continued*)

	Viral"[Mesh]) OR (sexually transmitted disease*[tiab] OR sexually transmissible disease*[tiab] OR sexually transmitted infection*[tiab] OR sexually transmissible infection*[tiab] OR sexually transmitted infectious disease*[tiab] OR sexually transmissible infectious disease*[tiab] OR sexually transmitted disorder*[tiab] OR sexually transmissible disorder*[tiab] OR STI[tiab] OR STD[tiab] OR genital ulcer*[tiab] OR genital ulcer disease*[tiab] OR genital infection*[tiab] OR genital disorder*[tiab] OR venereal disease*[tiab] OR venereal infection*[tiab] OR venereal disorder*[tiab]) OR ((sexually transmitted disease*[tiab]) AND (viral[tiab] OR bacterial[tiab] OR fungal[tiab] OR			disease*:ti OR sexually AND transmitted AND disease*:ab) OR (sexually AND transmissible AND disease*:ti OR sexually AND transmissible AND disease*:ab) OR (sexually AND transmitted AND infection*:ti OR sexually AND transmitted AND infection*:ab) OR (sexually AND transmissible AND infection*:ti OR sexually AND transmissible AND infection*:ab) OR (sexually AND transmitted AND infectious AND disease*:ti OR sexually AND transmitted AND infectious AND disease*:ab) OR (sexually AND transmissible AND infectious AND disease*:ti OR sexually AND transmissible AND infectious AND disease*:ab) OR (sexually AND transmitted AND disorder*:ti OR sexually AND transmitted AND disorder*:ab) OR (sexually AND transmissible AND disorder*:ti OR sexually AND transmissible AND disorder*:ab) OR sti:ti OR sti:ab OR std:ti OR std:ab OR (genital AND ulcer*:ti OR genital AND ulcer*:ab) OR (genital AND 'ulcer'/exp AND		

(*Continued*)

	protozoan[tiab])) OR ("Herpes Simplex"[Mesh] OR "Herpes Genitalis"[Mesh] OR herpes simplex[tiab] OR herpes genitalis[tiab] OR genital herpes[tiab] OR herpes virus[tiab] OR HSV-1[tiab] OR HSV-2[tiab]) OR ("Gonorrhea"[Mesh] OR gonorrhea[tiab] OR neisseria gonorrhoeae[tiab] OR gonococcal urethritis[tiab] OR gonococcal urethritis[tiab] OR gonococci[tiab]) OR ("Syphilis"[Mesh] OR syphilis[tiab] OR treponema pallidum[tiab] OR chancre[tiab] OR primary syphilis[tiab] OR secondary syphilis[tiab] OR condylomata lata[tiab]) OR ("Candida albicans"[Mesh] OR candida albicans[tiab] OR monilia albicans[tiab] OR monilial infection[tiab] OR candidiasis[tiab] OR candida[tiab] OR candidal vaginitis[tiab]			disease*:ti OR genital AND 'ulcer'/exp AND disease*:ab) OR (genital AND infection*:ti OR genital AND infection*:ab) OR (genital AND disorder*:ti OR genital AND disorder*:ab) OR (venereal AND disease*:ti OR venereal AND disease*:ab) OR (venereal AND infection*:ti OR venereal AND infection*:ab) OR (venereal AND disorder*:ti OR venereal AND disorder*:ab) OR (sexually AND transmitted AND disease*:ti OR sexually AND transmitted AND disease*:ab AND (viral:ti OR viral:ab)) OR bacterial:ti OR bacterial:ab OR fungal:ti OR fungal:ab OR protozoan:ti OR protozoan:ab OR 'herpes simplex'/exp OR 'herpes genitalis'/exp OR ('herpes'/exp AND simplex:ti OR 'herpes'/exp AND simplex:ab) OR ('herpes'/exp AND genitalis:ti OR 'herpes'/exp AND genitalis:ab) OR (genital AND herpes:ti OR genital AND herpes:ab) OR ('herpes'/exp AND virus:ti OR 'herpes'/exp AND virus:ab) OR 'hsv 1':ti OR 'hsv 1':ab OR 'hsv 2':ti OR 'hsv 2':ab OR 'gonorrhea'/		

(*Continued*)

	OR candidosis[tiab] OR vulvovaginitis[tiab] OR vulvitis[tiab] OR vulvovaginal candidiasis[tiab] OR vulvodynia[tiab] OR balanitis[tiab]) OR ("Chlamydia trachomatis"[Mesh] OR "Lymphogranuloma Venereum"[Mesh] OR lymphogranuloma venereum[tiab] OR chlamydia trachomatis[tiab] OR chlamydia infections[tiab] OR LGV[tiab]) OR ("Human papillomavirus 6"[Mesh] OR "Human papillomavirus 18"[Mesh] OR "Human papillomavirus 11"[Mesh] OR "Human papillomavirus 16"[Mesh] OR "Papillomavirus Infections"[Mesh] OR human papillomavirus[tiab] OR cervical cancer[tiab] OR HPV[tiab] OR genital wart*[tiab] OR anogenital wart*[tiab] OR anorectal wart*[tiab]			exp OR gonorrhea:ti OR gonorrhea:ab OR ('neisseria'/exp AND gonorrhoeae:ti OR 'neisseria'/exp AND gonorrhoeae:ab) OR (gonococcal AND urethritis:ti OR gonococcal AND urethritis:ab) OR gonococci:ti OR gonococci:ab OR 'syphilis'/exp OR syphilis:ti OR syphilis:ab OR ('treponema'/exp AND pallidum:ti OR 'treponema'/exp AND pallidum:ab) OR chancre:ti OR chancre:ab OR (primary AND syphilis:ti OR primary AND syphilis:ab) OR (secondary AND syphilis:ti OR secondary AND syphilis:ab) OR ('condylomata'/exp AND lata:ti OR 'condylomata'/exp AND lata:ab) OR 'candida albicans'/exp OR ('candida'/exp AND albicans:ti OR 'candida'/exp AND albicans:ab) OR ('monilia'/exp AND albicans:ti OR 'monilia'/exp AND albicans:ab) OR (monilial AND infection:ti OR monilial AND infection:ab) OR (candidiasis:ti OR monilial AND infection:ab) OR candida:ti OR (candidal AND vaginitis:ti) OR candida:ab OR candidosis:ti OR		

(*Continued*)

	OR anorectal wart*[tiab] OR penile wart*[tiab] OR condylomata acuminata[tiab] OR condyloma[tiab]) OR ("Vaginosis, Bacterial"[Mesh] OR "Gardnerella"[Mesh] OR "Gardnerella vaginalis"[Mesh] OR "Mobiluncus"[Mesh] OR bacterial vaginosis[tiab] OR gardnerella vaginalis[tiab] OR bacterial vaginitis[tiab] OR vaginitis[tiab] OR vaginosis[tiab]))			candidosis:ab OR vulvovaginitis:ti OR vulvovaginitis:ab OR vulvitis:ti OR vulvitis:ab OR (vulvovaginal AND candidiasis:ti OR vulvovaginal AND candidiasis:ab) OR vulvodynia:ti OR vulvodynia:ab OR balanitis:ti OR balanitis:ab OR 'chlamydia trachomatis'/exp OR 'lymphogranuloma venereum'/exp OR (lymphogranuloma AND venereum:ti OR lymphogranuloma AND venereum:ab) OR ('chlamydia'/exp AND trachomatis:ti OR 'chlamydia'/exp AND trachomatis:ab) OR ('chlamydia'/exp AND infections:ti OR 'chlamydia'/exp AND infections:ab) OR lgv:ti OR lgv:ab OR 'human papillomavirus 6'/exp OR 'human papillomavirus 18'/exp OR 'human papillomavirus 11'/exp OR 'human papillomavirus 16'/exp OR 'papillomavirus infections'/exp OR ('human'/exp AND papillomavirus:ti OR 'human'/exp AND papillomavirus:ab) OR (cervical AND cancer:ti OR cervical AND cancer:ab) OR hpv:ti OR hpv:ab OR (genital AND wart*:ti OR genital AND wart*:ab)		

(*Continued*)

				OR (anogenital AND wart*:ti OR anogenital AND wart*:ab) OR (anorectal AND wart*: ti OR anorectal AND wart*:ab) OR (penile AND wart*:ti OR penile AND wart*:ab) OR ('condylomata'/ exp AND acuminata: ti OR 'condylomata'/ exp AND acuminata: ab) OR condyloma:ti OR condyloma:ab OR 'vaginosis, bacterial'/ exp OR 'gardnerella'/ exp OR 'gardnerella vaginalis'/exp OR 'mobiluncus'/exp OR (bacterial AND vaginosis:ti OR bacterial AND vaginosis:ab) OR ('gardnerella'/ exp AND vaginalis: ti OR 'gardnerella'/ exp AND vaginalis:ab) OR (bacterial AND vaginitis:ti OR bacterial AND vaginitis: ab) OR vaginitis:ti OR vaginitis:ab OR vaginosis:ti OR vaginosis: ab AND [embase]/lim		
#2	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human	05:01:55	251,237	'human immunodeficiency virus infection'/ exp OR 'human immunodefi- ciency virus infection'/ de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/ exp OR 'human immunodeficiency virus'/ de OR 'human immunodeficiency virus' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab	299435	4 Dec 2009

(*Continued*)

	immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw]))			OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab		
#3	Search #1 OR #2	05:02:13	436,499	#1 OR #2	890060	4 Dec 2009
#4	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR	05:02:29	2178067	random*: ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over*:ab OR crossover*:ti OR crossover*: ab OR placebo*:ti OR placebo*: ab OR (doubl*:ti AND	731483	4 Dec 2009

(*Continued*)

	trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])			blind*:ti) OR (doubl*: ab AND blind*:ab) OR (singl*:ti AND blind*: ti) OR (singl*:ab AND blind*:ab) OR assign*: ti OR assign*:ab OR allocat*:ti OR allocat*: ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/ exp OR 'crossover proce- dure'/de OR 'crossover procedure' OR 'double-blind procedure'/exp OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/exp OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomized controlled trial'/ exp OR 'randomized controlled trial'/de OR 'randomized controlled trial' AND [embase]/ lim		
#5	Search ((microbicid*[tiab] OR spermicid*[tiab]) OR ((topical[tiab]) OR (vaginal[tiab]) OR (rectal[tiab]) AND (microbicid*[tiab])) OR ((antimicrobial[tiab]) AND (vaginal[tiab]) OR (rectal[tiab])))	05:02:43	54,632	microbicid*:ti OR microbicid* OR spermicid*:ti OR spermicid* OR (topical:ti OR 'topical'/exp OR vaginal:ti OR vaginal OR rectal: ti OR 'rectal'/exp AND (microbicid*:ti OR microbicid*)) OR (antimicrobial:ti OR 'antimicrobial'/exp AND (vaginal:ti OR vaginal)) OR rectal:ti OR 'rectal'/exp AND [embase]/lim	41022	4 Dec 2009
#6	Search #3 AND # 4 AND #5	05:03:04	851	#3 AND #4 AND #5	1005	4 Dec 2009

(*Continued*)

#7	Search ("1980/01/01"[Publication Date] : "2009/12/04"[Publication Date]) AND (#3 AND #4 AND #5)	05:03:29	822	#3 AND #4 AND #5 AND [humans]/lim AND [embase]/lim AND [1980-2009]/py	875	4 Dec 2009

Appendix 3. Search strings, HIV Review Group 2011

Table 6. (PubMed, EMBASE)

PubMed				EMBASE			
Search	Most Recent Queries	Time	Result	No.	Query	Results	Date
#1	Search (("Sexually Transmitted Diseases"[Mesh] OR "Sexually Transmitted Diseases, Bacterial"[Mesh] OR "Sexually Transmitted Diseases, Viral"[Mesh]) OR (sexually transmitted disease*[tiab] OR sexually transmissible disease*[tiab] OR sexually transmitted infection*[tiab] OR sexually transmissible infection*[tiab] OR sexually transmitted infectious	06:42:54	396,929	**#1**	'sexually transmitted diseases'/exp OR 'sexually transmitted diseases, bacterial'/exp OR 'sexually transmitted diseases, viral'/exp OR (sexually AND transmitted AND disease*:ti OR sexually AND transmitted AND disease*:ab) OR (sexually AND transmissible AND disease*:ti OR sexually AND transmissible AND disease*:ab) OR (sexually AND transmitted AND infection*:ti OR sexually AND transmitted AND infection*:ab) OR (sexually AND transmissible		

(*Continued*)

	disease*[tiab] OR sexually transmissible infectious disease*[tiab] OR sexually transmitted disorder*[tiab] OR sexually transmissible disorder*[tiab] OR STI[tiab] OR STD[tiab] OR genital ulcer*[tiab] OR genital ulcer disease*[tiab] OR genital infection*[tiab] OR genital disorder*[tiab] OR venereal disease*[tiab] OR venereal infection*[tiab] OR venereal disorder*[tiab]) OR ((sexually transmitted disease*[tiab]) AND (viral[tiab] OR bacterial[tiab] OR fungal[tiab] OR protozoan[tiab])) OR ("Herpes Simplex"[Mesh] OR "Herpes Genitalis"[Mesh] OR herpes simplex[tiab] OR herpes genitalis[tiab]				AND infection*:ti OR sexually AND transmissible AND infection*:ab) OR (sexually AND transmitted AND infectious AND disease*:ti OR sexually AND transmitted AND infectious AND disease*:ab) OR (sexually AND transmissible AND infectious AND disease*:ti OR sexually AND transmissible AND infectious AND disease*:ab) OR (sexually AND transmitted AND disorder*:ti OR sexually AND transmitted AND disorder*:ab) OR (sexually AND transmissible AND disorder*:ti OR sexually AND transmissible AND disorder*:ab) OR sti:ti OR sti:ab OR std:ti OR std:ab OR (genital AND ulcer*:ti OR genital AND ulcer*:ab) OR (genital AND 'ulcer'/exp AND disease*:ti OR genital AND 'ulcer'/exp AND disease*:ab) OR (genital AND infection*:ti OR genital AND infection*:ab) OR (genital AND disor-		

(*Continued*)

	OR genital herpes[tiab] OR herpes virus[tiab] OR HSV-1[tiab] OR HSV-2[tiab]) OR ("Gonorrhea"[Mesh] OR gonorrhea[tiab] OR neisseria gonorrhoeae[tiab] OR gonococcal urethritis[tiab] OR gonococcal urethritis[tiab] OR gonococci[tiab]) OR ("Syphilis"[Mesl OR syphilis[tiab] OR treponema pallidum[tiab] OR chancre[tiab] OR primary syphilis[tiab] OR secondary syphilis[tiab] OR condylomata lata[tiab]) OR ("Candida albicans"[Mesh] OR candida albicans[tiab] OR monilia albicans[tiab] OR monilial infection[tiab] OR candidiasis[tiab] OR candida[tiab] OR candidal vaginitis[tiab]				der*:ti OR genital AND disorder*:ab) OR (venereal AND disease*:ti OR venereal AND disease*:ab) OR (venereal AND infection*:ti OR venereal AND infection*:ab) OR (venereal AND disorder*:ti OR venereal AND disorder*:ab) OR (sexually AND transmitted AND disease*:ti OR sexually AND transmitted AND disease*:ab AND (viral:ti OR viral:ab)) OR bacterial:ti OR bacterial:ab OR fungal:ti OR fungal:ab OR protozoan:ti OR protozoan:ab OR 'herpes simplex'/exp OR 'herpes genitalis'/exp OR ('herpes'/exp AND simplex:ti OR 'herpes'/exp AND simplex:ab) OR ('herpes'/exp AND genitalis:ti OR 'herpes'/exp AND genitalis:ab) OR (genital AND herpes:ti OR genital AND herpes:ab) OR ('herpes'/exp AND virus:ti OR 'herpes'/exp AND virus:ab) OR 'hsv 1':ti OR 'hsv 1':ab OR 'hsv 2':ti OR 'hsv 2':ab OR 'gonorrhea'/		

(*Continued*)

	OR candidosis[tiab] OR vulvovaginitis[tiab] OR vulvitis[tiab] OR vulvovaginal candidiasis[tiab] OR vulvodynia[tiab] OR balanitis[tiab]) OR ("Chlamydia trachomatis"[Mesh] OR "Lymphogranuloma Venereum"[Mes OR lymphogranuloma venereum[tiab] OR chlamydia trachomatis[tiab] OR chlamydia infections[tiab] OR LGV[tiab]) OR ("Human papillomavirus 6"[Mesh] OR "Human papillomavirus 18"[Mesh] OR "Human papillomavirus 11"[Mesh] OR "Human papillomavirus 16"[Mesh] OR "Papillomavirus Infections"[Mesh] OR human papillomavirus[tiab] OR cervical cancer[tiab] OR HPV[tiab]				exp OR gonorrhea:ti OR gonorrhea:ab OR ('neisseria'/exp AND gonorrhoeae:ti OR 'neisseria'/exp AND gonorrhoeae:ab) OR (gonococcal AND urethritis:ti OR gonococcal AND urethritis:ab) OR gonococci:ti OR gonococci:ab OR 'syphilis'/exp OR syphilis:ti OR syphilis:ab OR ('treponema'/exp AND pallidum:ti OR 'treponema'/exp AND pallidum:ab) OR chancre:ti OR chancre:ab OR (primary AND syphilis:ti OR primary AND syphilis:ab) OR (secondary AND syphilis:ti OR secondary AND syphilis:ab) OR ('condylomata'/exp AND lata:ti OR 'condylomata'/exp AND lata:ab) OR 'candida albicans'/exp OR ('candida'/exp AND albicans:ti OR 'candida'/exp AND albicans:ab) OR ('monilia'/exp AND albicans:ti OR 'monilia'/exp AND albicans:ab) OR (monilial AND infection:ti OR monilial AND infection:ab) OR (candidiasis:		

(*Continued*)

	OR genital wart*[tiab] OR anogenital wart*[tiab] OR anorectal wart*[tiab] OR anorectal wart*[tiab] OR penile wart*[tiab] OR condylomata acuminata[tiab] OR condyloma[tiab]) OR ("Vaginosis, Bacterial"[Mesh] OR "Gardnerella"[Mesh] OR "Gardnerella vaginalis"[Mesh] OR "Mobiluncus"[Mesh] OR bacterial vaginosis[tiab] OR gardnerella vaginalis[tiab] OR bacterial vaginitis[tiab] OR vaginitis[tiab] OR vaginosis[tiab]))				ti OR monilial AND infection:ab) OR candida:ti OR (candidal AND vaginitis:ti) OR candida:ab OR candidosis:ti OR candidosis:ab OR vulvovaginitis:ti OR vulvovaginitis:ab OR vulvitis:ti OR vulvitis:ab OR (vulvovaginal AND candidiasis:ti OR vulvovaginal AND candidiasis:ab) OR vulvodynia:ti OR vulvodynia:ab OR balanitis:ti OR balanitis:ab OR 'chlamydia trachomatis'/exp OR 'lymphogranuloma venereum'/exp OR (lymphogranuloma AND venereum:ti OR lymphogranuloma AND venereum:ab) OR ('chlamydia'/exp AND trachomatis:ti OR 'chlamydia'/exp AND trachomatis:ab) OR ('chlamydia'/exp AND infections:ti OR 'chlamydia'/exp AND infections:ab) OR lgv:ti OR lgv:ab OR 'human papillomavirus 6'/exp OR 'human papillomavirus 18'/exp OR 'human papillomavirus 11'/exp OR 'human		

(*Continued*)

					papillomavirus 16'/exp OR 'papillomavirus infections'/exp OR ('human'/exp AND papillomavirus:ti OR 'human'/exp AND papillomavirus:ab) OR (cervical AND cancer:ti OR cervical AND cancer:ab) OR hpv:ti OR hpv:ab OR (genital AND wart*:ti OR genital AND wart*:ab) OR (anogenital AND wart*:ti OR anogenital AND wart*:ab) OR (anorectal AND wart*:ti OR anorectal AND wart*:ab) OR (penile AND wart*:ti OR penile AND wart*:ab) OR ('condylomata'/exp AND acuminata:ti OR 'condylomata'/exp AND acuminata:ab) OR condyloma:ti OR condyloma:ab OR 'vaginosis, bacterial'/exp OR 'gardnerella'/exp OR 'gardnerella vaginalis'/exp OR 'mobiluncus'/exp OR (bacterial AND vaginosis:ti OR bacterial AND vaginosis:ab) OR ('gardnerella'/exp AND vaginalis:ti OR 'gardnerella'/exp AND vaginalis:		

(*Continued*)

					ab) OR (bacterial AND vaginitis: ti OR bacterial AND vaginitis: ab) OR vaginitis: ti OR vaginitis:ab OR vaginosis:ti OR vaginosis:ab		
#2	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immuned-eficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immuned-eficiency syndrome[tw]	06:43:19	274,560	**#2**	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immunodeficiency virus': ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':	353899	22 Jul 2011

(*Continued*)

	OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])))				ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immuned-eficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab		
#3	Search #1 OR #2	06:43:33	476,207	#3	#1 OR #2	959369	22 Jul 2011
#4	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	06:43:49	2418927	#4	random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over*:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR allocat*:ti OR allocat*:ab OR volunteer*:	1111594	22 Jul 2011

(*Continued*)

					ti OR volunteer*:ab OR 'crossover procedure'/exp OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/exp OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/exp OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomized controlled trial'/exp OR 'randomized controlled trial'/de OR 'randomized controlled trial'		
#5	Search ((microbicid*[tiab] OR spermicid*[tiab]) OR ((topical[tiab]) OR (vaginal[tiab]) OR (rectal[tiab]) AND (microbicid*[tiab])) OR ((antimicrobial[tiab]) AND (vaginal[tiab]) OR (rectal[tiab]))))	06:44:07	59,984	#5	microbicid*:ti OR microbicid* OR spermicid*:ti OR spermicid* OR (topical:ti OR 'topical'/exp OR vaginal:ti OR vaginal OR rectal:ti OR 'rectal'/exp AND (microbicid*:ti OR microbicid*)) OR (antimicrobial:ti OR 'antimicrobial'/exp AND (vaginal:ti OR vaginal)) OR rectal:ti OR 'rectal'/exp	59995	22 Jul 2011
#6	Search #3 AND #4 AND #5	06:44:22	1010	#6	#3 AND #4 AND #5	1455	22 Jul 2011
#7	Search #3 AND #4 AND #5 Lim-	08:39:46	162				

(*Continued*)

	its: Publication Date from 2009/11/01 to 2011/07/22						
				#8	#3 AND #4 AND #5 AND [humans]/lim AND [embase]/lim AND [2009-2011]/py	175	22 Jul 2011

Table 7. (CLIB)

#1	MeSH descriptor Sexually Transmitted Diseases explode all trees
#2	sexually transmitted disease*:ti,ab,kw OR sexually transmissible disease*:ti,ab,kw OR sexually transmitted infection*:ti,ab,kw OR sexually transmissible infection*:ti,ab,kw OR sexually transmitted infectious disease*:ti,ab,kw OR sexually transmissible infectious disease*:ti,ab,kw OR sexually transmitted disorder*:ti,ab,kw OR sexually transmissible disorder*:ti,ab,kw OR STI:ti,ab,kw OR STD:ti,ab,kw OR genital ulcer*:ti,ab,kw OR genital ulcer disease*:ti,ab,kw OR genital infection*:ti,ab,kw OR genital disorder*:ti,ab,kw OR venereal disease*:ti,ab,kw OR venereal infection*:ti,ab,kw OR venereal disorder*:ti,ab,kw
#3	(sexually transmitted disease*:ti,ab,kw) AND (viral:ti,ab,kw OR bacterial:ti,ab,kw OR fungal:ti,ab,kw OR protozoan:ti,ab,kw)
#4	herpes simplex:ti,ab,kw OR herpes genitalis:ti,ab,kw OR genital herpes:ti,ab,kw OR herpes virus:ti,ab,kw OR HSV-1:ti,ab,kw OR HSV-2:ti,ab,kw
#5	gonorrhea:ti,ab,kw OR neisseria gonorrhoeae:ti,ab,kw OR gonococcal urethritis:ti,ab,kw OR gonococcal urethritis:ti,ab,kw OR gonococci:ti,ab,kw
#6	syphilis:ti,ab,kw OR treponema pallidum:ti,ab,kw OR chancre:ti,ab,kw OR primary syphilis:ti,ab,kw OR secondary syphilis:ti,ab,kw OR condylomata lata:ti,ab,kw
#7	candida albicans:ti,ab,kw OR monilia albicans:ti,ab,kw OR monilial infection:ti,ab,kw OR candidiasis:ti,ab,kw OR candida:ti,ab,kw OR candidal vaginitis:ti,ab,kw OR candidosis:ti,ab,kw OR vulvovaginitis:ti,ab,kw OR vulvitis:ti,ab,kw OR vulvovaginal candidiasis:ti,ab,kw OR vulvodynia:ti,ab,kw OR balanitis:ti,ab,kw
#8	lymphogranuloma venereum:ti,ab,kw OR chlamydia trachomatis:ti,ab,kw OR chlamydia infections:ti,ab,kw OR LGV:ti,ab,kw
#9	human papillomavirus:ti,ab,kw OR cervical cancer:ti,ab,kw OR HPV:ti,ab,kw OR genital wart*:ti,ab,kw OR anogenital wart*:ti,ab,kw OR anorectal wart*:ti,ab,kw OR anorectal wart*:ti,ab,kw OR penile wart*:ti,ab,kw OR condylomata acuminata:ti,ab,kw OR condyloma:ti,ab,kw
#10	human papillomavirus:ti,ab,kw OR cervical cancer:ti,ab,kw OR HPV:ti,ab,kw OR genital wart*:ti,ab,kw OR anogenital wart*:ti,ab,kw OR anorectal wart*:ti,ab,kw OR anorectal wart*:ti,ab,kw OR penile wart*:ti,ab,kw OR condylomata acuminata:ti,

(*Continued*)

	ab,kw OR condyloma:ti,ab,kw
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12	MeSH descriptor Herpes Genitalis, this term only
#13	MeSH descriptor Gonorrhea explode all trees
#14	MeSH descriptor Candida albicans, this term only
#15	MeSH descriptor Chlamydia trachomatis, this term only
#16	MeSH descriptor Lymphogranuloma Venereum explode all trees
#17	MeSH descriptor Papillomavirus Infections explode all trees
#18	MeSH descriptor Human papillomavirus 16, this term only
#19	MeSH descriptor Vaginosis, Bacterial explode all trees
#20	MeSH descriptor Gardnerella explode all trees
#21	(#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22	(#11 OR #21)
#23	MeSH descriptor HIV explode all trees
#24	MeSH descriptor HIV Infections explode all trees
#25	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME
#26	MeSH descriptor Lymphoma, AIDS-Related, this term only
#27	(#23 OR #24 OR #25 OR #26)
#28	(#22 OR #27)
#29	microbicid*:ti,ab,kw OR spermicid*:ti,ab,kw
#30	(topical:ti,ab,kw OR vaginal:ti,ab,kw OR rectal:ti,ab,kw) AND (microbicid*:ti,ab,kw OR spermicid*:ti,ab,kw)
#31	(antimicrobial:ti,ab,kw) AND (vaginal:ti,ab,kw OR rectal:ti,ab,kw)

(*Continued*)

#32	(#29 OR #30 OR #31)
#33	(#28 AND #32)
#34	(#28 AND #32), from 2009 to 2011

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 6, 2012

CONTRIBUTIONS OF AUTHORS

Jael Obiero and Charles Shey Wiysonge conceived the review and all three review authors participated in the development of the protocol and the preparation of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- South African Medical Research Council (CSW), South Africa.
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External sources

- Reviews for Africa Program, South African Medical Research Council (JAO), South Africa.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have removed controlled clinical trials from study eligibility criteria and included type participants in the objective of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acrylic Resins [administration & dosage]; Adenine [administration & dosage; analogs & derivatives]; Administration, Topical; Agaricales [chemistry]; Anti-HIV Agents; Anti-Infective Agents, Local [*administration & dosage]; Cellulose [administration & dosage; analogs & derivatives]; HIV Infections [prevention & control]; Naphthalenesulfonates [administration & dosage]; Organophosphonates [administration & dosage]; Polymers [administration & dosage]; Seaweed [chemistry]; Sexually Transmitted Diseases [* prevention & control]

MeSH check words

Female; Humans; Male