The Efficacy and Safety of Topical Microbicide Gels to Prevent Sexual Transmission of Human Immunodeficiency Virus (HIV) Infection: a Systematic Review and Meta-analysis

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Abstract

Background: Topical microbicide gels are a potential method to reduce sexually transmitted human immunodeficiency virus (HIV) infection, especially in women. Several randomized controlled trials (RCTs) of topical microbicides to prevent HIV transmission have yielded promising results, however trial results have been inconsistent. The objective of this study was to determine the efficacy and safety of topical microbicide gels to prevent HIV transmission.

Methods: We conducted meta-analyses, stratified by microbicide gel type, using a random-effects model. We included 25 RCTs that met the inclusion criteria: 13 RCTs examined gel efficacy during heterosexual contact, and an additional 12 trials reported on gel acceptability, participants' adherence to intervention, and adverse reactions (allergic reaction and pain).

Results: With this limited data, topical microbicide gels were not found to be significantly better than placebo in preventing HIV infection (risk ratio (RR) 0.93, 95% CI 0.82 to 1.04; I^2 14%; 13 trials; 31,764 participants). It should be noted that low adherence rates were frequently reported within trials. In one trial with high participant adherence (>70%) to intervention, there was a significant protective effect of gels (RR 0.63, 95% CI 0.43 to 0.93; 889 participants). While measures of acceptability and adherence to intervention were similar between groups, administration of topical microbicides were associated with an increased incidence of pain at the application site (RR 1.16, 95% CI 1.00 to 1.36, I^2 0%, 15 trials, 19,554 participants).

Conclusions: In conclusion, efficacy of topical microbicide gels may relate to baseline risk and compliance with the intervention. In the general population it is not associated with protection from sexually transmitted HIV infection.

Introduction

Globally, human immunodeficiency virus (HIV) affects over 38 million people, with 2.1 million new infections diagnosed in 2015 (1). Women are disproportionately affected by the HIV epidemic in Africa; the continent that accounts for more than 70% of the global burden of HIV (2). Unprotected sexual contact is responsible for the majority of new cases worldwide, and a clear need exists for new technologies to prevent HIV transmission, particularly methods that are female controlled methods.

As there is currently no cure for HIV, nor vaccine to prevent infection, the control of the HIV epidemic is dependent upon other biomedical, behavioural and structural prevention interventions, and life-long treatment regimens for those that are infected; all of which have substantial individual, social and economic impacts (3). Currently, HIV prevention includes education and awareness of HIV risk factors, promotion of condom use, the use of pre-exposure prophylaxis, male circumcision, and structural interventions such as violence reduction (4). These practices, however, are largely partner-dependent, and barriers to use can limit their impact on incidence rates in women, especially in sub-Saharan Africa where young women bear the greatest HIV burden (4). Additional strategies to prevent the spread of HIV, particularly those that women can use and control, remain a pressing priority (5).

Topical microbicide gels are applied to the vagina or rectum pre-exposure with the intention of reducing sexually transmitted HIV. These gels may potentially prevent both male-to-female and female-to-male transmission. If proven effective and safe, topical microbicide gels would be an important addition to the prevention toolkit. In phase I clinical trials, topically applied microbicide gels were shown to be acceptable and well tolerated by both HIV-negative and -positive women (6–12). However, the efficacy and safety of topical gels to prevent sexual transmission of HIV remains uncertain.

The objective of this systematic review is to identify, critically appraise and meta-analyze data from randomized trials evaluating topical microbicide gels to prevent sexually transmitted HIV infection.

Methods

We followed a published, a priori protocol (13) and conducted this systematic review in accordance to the Methodological Expectations of Cochrane Intervention Reviews (14). Reporting is in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15).

Populations, Interventions, Comparators, Outcome Measures, and Study Designs

We included only randomized, controlled trials of sexually active adult participants who were not found to be HIV positive. Our primary research question was “What is the safety and efficacy of topical microbicide gels to prevent sexually transmitted HIV infection?” The main outcome measure was laboratory confirmed HIV infection. Secondary outcomes included patient adherence to intervention, and patient acceptability of intervention. Safety outcomes included allergic reaction and pain at application site. Inclusion and exclusion criteria are presented in the appendices.

Search strategy for identification of studies

We searched MEDLINE (Ovid), EMBASE (Ovid), and CENTRAL (Cochrane Library – Wiley) from inception to March 2019 using individualized search strategies prepared for each database using the Cochrane Highly Sensitive Search Strategy as a model. The MEDLINE search, which was reviewed by a second information specialist using the Peer Review for Electronic Search Strategies (PRESS) template (16) is presented in the Appendix. To identify additional relevant citations, we performed a forward search in Scopus and Web of Science. To identify ongoing or planned trials we searched the World Health Organization’s International Clinical Trials Registry Platform.

We searched abstracts and conference proceedings (2011–2019) for the following societies: British HIV Association, Conference on Retroviruses and Opportunistic Infections, The International Society for Sexually Transmitted Disease Research, International AIDS Society, Forum for Collaborative HIV Research, Canadian Association for HIV Research and UNAIDS. Reference lists of relevant narrative and systematic reviews and included trials were hand-searched for possible relevant citations. Reference Management was performed in EndNote™ (ver. X7, Thompson Reuters, 2016, New York, NY, USA).

We used a two-step process for study selection. First, two reviewers (JG and SV) independently screened the titles and abstracts (when available) of search results to determine if a study met the general inclusion criteria. The full texts of relevant citations were then reviewed in duplicate to determine eligibility of inclusion. Data from trial reports were extracted in duplicate (JG, SV, TA) using a standardized form and entered into a Microsoft Excel™ database (Microsoft Corp., Redmond, WA).

The following data were extracted from each trial: author identification, year of publication, language of publication, source of study funding, study design, risk of bias criteria (see below), study population (including study inclusion and exclusion criteria), patient characteristics (e.g. age, sex, HIV status, sexually transmitted infection status), intervention and its comparator, and results reported for the outcomes of interest. As needed, authors were contacted for further information about their trials. For both study selection and data extraction, disagreements were resolved by discussion between the two reviewers or by third-party adjudication (AMAS), if required.

Risk of Bias Assessment

The internal validity of trials was assessed by using the Cochrane Collaboration Risk of Bias tool (17, 18). This tool consists of six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias) and a categorization of the overall risk of bias. Information regarding risk of bias was used to guide sensitivity analyses and explore sources of heterogeneity.

Measures of Intervention Effect

The data from the included trials was analyzed using Review Manager (RevMan version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Pooled dichotomous data is presented as a risk ratio (RR) with 95% confidence intervals (CI). Statistical heterogeneity was explored and quantified using the I-squared statistic (19).

Subgroup Analyses

To determine summary effect estimates in several strata, including: type of microbicide used, participant adherence to intervention, and participant demographics (women at high risk of HIV infection, women at low/moderate risk of HIV infection).

Publication Bias

Publication bias was assessed using funnel plot techniques, as appropriate, given the known limitations of these methods (20).

Results

Trial Characteristics & Study Populations

Of 1,947 records identified from electronic and hand searches, we included 25 unique RCTs (36,319 participants) that met our inclusion criteria (Fig. 1). Of these, 13 trials (31,764 participants) evaluated the efficacy to prevent sexually transmitted HIV infection of seven different microbicide gels (21–33). These trials included strictly female participants and evaluated HIV transmission during heterosexual contact. None of these trials assessed the efficacy of topical microbicide gels to prevent HIV transmission during anal sex. The Van Damme 2008 (27) and Halpern 2008 (25) Cellulose Sulphate (CS) trials were stopped early after the Data Safety Monitoring Board (DSMB) determined that the CS gel may increase the risk of HIV infection when compared with placebo. A single trial of 2% PRO 2000 (34), a single trial of Tenofovir (32) and two SAVVY trials (23, 24) were stopped early due to low event rates.

We included twelve additional trials reporting on the secondary and safety outcomes of interest. Overall, nine trials (28, 29, 35–41) evaluated **gel acceptability** (1,758 participants), 7 trials (21, 28, 31, 36, 40, 42, 43) evaluated **participants' adherence to intervention** (2,417 participants), 20 trials (21, 23–28, 30–36, 38, 40, 41, 43–45) evaluated **allergic reaction** (31,605 participants) and 15 trials (21, 23, 24, 28, 29, 31, 32, 34–37, 41, 43, 45, 46) evaluated **pain** (19,555 participants).

The age of trial participants included in this review ranged from 16 to 72 years. Twenty-three of the trials (21, 23–34, 36, 39, 41–46) included female participants only. Five trials (21–25) identified their participants as being at high risk of HIV infection); one trial (37) enrolled heterosexual couples (although only reported on outcomes of interest from female participants); and one trial (40) enrolled both males and females with a previous history of receptive anal intercourse (RAI). The two trials (35, 40) that assessed male participants examined secondary outcomes only. All trials counselled and supplied free condoms to all the 26,319 participants (100 males and 36 219 females). Participants were instructed to use these barrier methods for all acts of sexual intercourse regardless of gel use. One trial (40) instructed participants to abstain from RAI during the trial.

The type and dose of active ingredient, along with frequency of application varied across the included trials; however, a placebo gel was consistently used as the comparator. Eleven different microbicide gels were included, namely, cellulose sulphate (CS) (25, 27, 36); SAVVY (23, 24); PRO 2000 (30, 34); Buffer- Gel (30); Carraguard (26, 29, 37, 46); Viva Gel (31); Nonoxynol-9 (21, 40, 42, 44, 45); Dapirivine (39); Dextrin Sulphate (35); Polymer Gel (43); and Tenofovir (28, 32, 33, 40, 41). Of these, seven trials used two different anti-retroviral (ARV) gels, namely, Dapirivine, and Tenofovir and the other microbicides were non-ARV based.

Risk of bias of included studies

Overall, most trials (16/25) (21, 26, 27, 29, 31, 33, 35–38, 40–44, 46) were adjudicated to be of unclear risk of bias, while the remaining trials (23–25, 28, 30, 32–34, 45) were considered at low risk of bias. Most trials had adequate random sequence generation (20/25), allocation concealment (20/25) and blinding of outcome assessment (22/25), and low risk of attrition bias (24/25), however the majority were subject to unclear (16/25) risk of selective outcome reporting due to the unavailability of a protocol. Our judgments about the risk of bias in each included study are summarized in Fig. 2.

Primary Outcome – HIV infection

In the general female population, we found no evidence that topical microbicide gels modified the rate of new HIV infection (21, 23–30, 32–34, 42) (Risk Ratio (RR) 0.93, 95% CI 0.82 to 1.04; I^2 14%; 13 trials; 31,764 participants; Fig. 3). However, variability was seen across the sub-populations. In women at average-/ low-risk of HIV infection, microbicide gels were associated with a significant reduction in the risk of new HIV infections (RR 0.88, 95% CI 0.79 to 0.99; I^2 0%; 8 trials; 24,655 participants); while in women identified as being at high risk of HIV infection, topical microbicides did not reduce HIV infection (RR 1.14, 95% CI 0.85 to 1.52; I^2 8%; 5 trials; 7,109 participants). Further, in a subgroup analysis that considered if participant adherence modified treatment effect, we found that in one trial (889 participants identified as at average-/low-risk of HIV infection) where > 70% of participants complied with their instructed gel regimen, new HIV infections were significantly reduced (RR 0.63, 95% CI 0.43 to 0.93; Appendices

Figs. 1 and 2). The opposite was also evident wherein a single trial (892 participants identified as at high risk infection) reporting < 70% participant adherence, the microbicides were not associated with reduced rates of HIV infection (RR 1.29, 95% CI 0.90 to 1.86).

Secondary Outcomes

Acceptability

Acceptability data was presented for nine different trials (8 publications) (28, 29, 35–38, 40, 41). Acceptability was presented as the proportion (%) of participants that either liked the gel or would be likely to use it again. We found no statistically significant difference in acceptability between the intervention and control groups (RR 0.99, 95% CI 0.95 to 1.04; I^2 0%; 1,758 participants;).

Adherence

Adherence was reported in seven trials (21, 28, 31, 36, 40, 42, 43). Adherence was measured as the proportion of participants who followed their instructed intervention regimen. Reporting of participant adherence varied by trial; four trials (21, 40, 42, 43) used participant self-report, whereas three trials (28, 31, 36) use both self-report in addition to accounting for the number of used and unused applicators returned by participants. There was no clear association between the type of microbicide and adherence to intervention (versus placebo gel) (RR 0.99, 95% CI 0.94 to 1.04; I^2 0%; 2,417 participants).

Safety Outcomes

Topical microbicide gels were not associated with allergic reactions, reported as either allergic reaction to product or adverse events such as redness, itchiness, or inflammation in gel application area (21, 23–28, 30–36, 39–41, 43–45) (RR 1.05, 95% CI 0.96 to 1.14, I^2 6%, 18 trials, 29,545 participants). The administration of topical microbicides was associated with increased incidence of pain at application site (RR 1.16, 95% CI 1.00 to 1.36, I^2 0%, 15 trials, 19,554 participants). Of these fifteen trials (21, 23, 24, 29–32, 34–37, 41, 43, 45, 46) reporting pain, 3.5% of participants in the active gel groups reported pain in the application area, compared to 2.8% of participants in the placebo gel groups. However, neither group listed pain as a reason for discontinuation. Severity and/or type of pain were not reported in a consistent manner among trials.

Discussion

In this systematic review and meta-analysis, we found that topical microbicide gels did not provide a protective effect against the transmission of heterosexually acquired HIV infection. Our review provides a timely update to the 2012 Cochrane review that examined the efficacy of topical microbicide gels to prevent HIV and other sexually transmitted infections. This previous review included solely female participants, did not include the microbicide nonoxynol-9 and, most importantly, new evidence has become available since this review was published. Our review is also the first to address the efficacy of topical microbicide gels to prevent sexual transmission of HIV among women, in trials published up until March 2019 (capturing five new trials, involving 5 632 participants examining the primary outcome), in addition to evaluating gel acceptability, adherence, pain and allergic reaction among men and women.

Overall, no significant difference was found between the active and placebo groups in the incidence of HIV transmission, acceptability, adherence to intervention, or allergic reaction. While the application frequencies, mode of application, mode of microbicidal action, and placebos used in the included trials differed, the end result was expected to be the same (e.g. prophylaxis), and we do not believe there is a strong enough rationale to consider the treatments different. Furthermore, the results from the individual studies were not statically different from one other. After systematic evaluation of these new and extended trial results, we conclude that there is still insufficient evidence to recommend topical microbicides for the prevention of HIV transmission to the public. It is important to note that lack of efficacy may be due to low incidence of HIV within the tested populations; thereby needing a much larger sample size to detect a statistically significant difference between the groups.

At present, limited evidence suggests that average-/ low-risk females may benefit from a reduction in heterosexually acquired HIV with gel use. However, this subgroup consisted of five different active gels (Tenofovir, PRO 2000, Buffer Gel, Cellulose Sulphate, Carraguard) and none of these interventions showed a statistically significant reduction in HIV acquisition within their own subgroup of microbicide. It is important to note that this observational data was gathered using post-hoc risk analysis and should

be used for hypothesis generation rather than confirmation. Our findings identify several unanswered questions and highlight opportunities for future research; for instance, the need to further consider the impact of participant adherence to intervention on microbicide efficacy. High participant adherence to intervention was associated with a statistically significant protective effect, however this was only demonstrated in one trial. Further research should continue the development and testing of new microbicides, as well as ways to support and measure adherence.

Above 70% participant adherence rates in the Karim 2010 trial (28) demonstrated an increased protective effect which emphasizes the need for purposeful research into maintaining participant adherence throughout trials. The successful launch of an effective gel will depend on having in place appropriate mechanisms for distribution to the women who need it, along with a strategy for ensuring is being used appropriately and effectively. It is critically important to note that low rates of adherence to study interventions by participants have been commonly stated as limitations in many of the included studies, despite overall acceptability of gels being high. While adherence may explain the possible lack of evidence to support the use of microbicides, it is not a key component of 'intention-to-treat'. Poor adherence rates may greatly affect the overall efficacy of potential topical microbicides in a real-world application. There are many examples of this including the use of IUD and injectable birth control rather than oral contraceptive pills for national programs even though the latter is more efficient. Compliance of daily intake of the intervention decreases its overall effectiveness.

Lastly, there was a statistically significant increase in reported pain at the application site with the active gels; however reported pain varied greatly between trials. An average of 3.5% of participants in the active gel groups reported pain at application site, which is still relatively low. Further research is needed to assess pain associated with use of specific types of active gels, and with increased frequency of gel usage. The strengths of this review include the completeness of the search strategy, including searching multiple citation databases, trial registries and conference abstracts. We focused on patient-centered outcomes and evaluated efficacy in the context of relevant safety outcomes and adverse events. Finally, we used an a priori published protocol and followed established methodological guidelines in the conduct and reporting of this review. This review is limited by the relatively high variability of risk of HIV acquisition between trial participants, which may restrict the broad generalizability of these findings. Additionally, the demographics of participants may not be representative of all populations at risk of acquiring HIV. Lastly, subgroup analyses were susceptible to type II errors due to relatively small sample sizes.

Authors' Conclusion

At present, the use of topical microbicide gels is not associated with protection from sexually transmitted HIV infection in the general population. As such, there is not enough evidence to recommend topical microbicide gels for regular use. Efficacy however might relate to baseline risk and compliance with the intervention. Further investigation into microbicide gels for HIV prevention should include targeted measures to increase adherence to intervention within specific subgroups (e.g. high-risk females, average-/low-risk females, men who have sex with men). Lastly, if microbicides are found to be effective, they would need to be incorporated into a broad comprehensive prevention program.

Declarations

Ethics approval:

Not applicable.

Consent to participate:

Not applicable.

Consent for publication:

All authors approved the manuscript and this submission.

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Conflicts of interest/Competing interests:

None of the authors have a commercial or other association that might pose a conflict of interest. There are no conflict of interests.

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Table

Table 1
Characteristics of Included Studies

Study ID	Intervention	Control	Demo-graphic	Age (mean)	Frequency of Application	Sample Size	Risk of Bias	Study Location
Bunge 2018	Tenofovir	HEC* Placebo Gel	Females	28	1x/ day	78	Unclear	USA
Carraguard Team	Carraguard Gel	Methylcellulose Placebo Gel	Females	27.8	3x/ week	400	Unclear	South Africa
Delany-Moretlwe 2018	Tenofovir Gel	Placebo Gel	Females	23	1x before and after every vaginal intercourse	2059	Unclear	South Africa
Doh 2007	Cellulose Sulphate Gel	KY Jelly	Females	Mid-20 s	4x/ day	54	Unclear	Cameroon
Feldblum 2008	SAVVY Gel	HEC Placebo Gel	High Risk Females	23.5 (3.7)	1x before each vaginal intercourse	2153	Low	Nigeria
Halpern 2008	Cellulose Sulphate Gel	HEC Placebo Gel	High Risk Females	23.4 (3.7)	1 hr. before every vaginal intercourse (within 24 hours)	1644	Low	Nigeria
Hoffman 2004	Nonoxynol-9 Gel	Placebo Gel	Females	29	2x/day	180	Unclear	Malawi, Zimbabwe
Karim 2010	Tenofovir Gel	HEC Placebo Gel	Females	24.2	1x before and after every vaginal intercourse (within 24 hours)	889	Low	South Africa
Karim 2011	PRO 2000/Buffer Gel	HEC Placebo Gel	Females	26.2	1x/ vaginal intercourse	2315	Low	Malawi, South Africa, Zambia, Zimbabwe, USA
Kilmarx 2006	Carraguard Gel	Methylcellulose Gel	Females	31.2	3x/week	165	Unclear	Thailand
Kilmarx 2008	Carraguard Gel	Methylcellulose Gel	Heterosexual Couples	33.71	1x before each vaginal intercourse (females only)	55 couples	Unclear	Thailand
Low-Beer 2002	Dextrin Sulphate Gel	Placebo Gel	Females	29	1x/day and 1x before vaginal intercourse	77	Unclear	United Kingdom

*HEC = hydroxyethylcellulose gel; *RAI = receptive anal intercourse

Study ID	Intervention	Control	Demo-graphic	Age (mean)	Frequency of Application	Sample Size	Risk of Bias	Study Location
Marrazzo 2015	Tenofovir Gel	HEC Placebo	Females	25.3 (5.2)	1x/day	2010	Low	South Africa, Uganda, Zimbabwe
Mbopi-Keou 2010	Polymer Gel and Polymer Gel with Sodium Laurel Sulphate	HEC Placebo Gel	Females	30	2x/day	194	Unclear	Cameroon
McCormack 2010	PRO 2000	HEC Placebo Gel	Females	N/A	1 hr before each vaginal intercourse	9385	Low	South Africa, Tanzania, Uganda
McGowan 2011	Viva Gel	Viva Gel Placebo	Females	20.8 (1.5)	2x/day	43	Unclear	United States of America, Puerto Rico
McGowan 2012	Tenofovir & Nonoxynol - 9 Gel	HEC Placebo Gel	Males & Females with a history of RAI*	35.7	1x/day	65	Unclear	United States of America
Nel 2009 (IPM003)	Dapivirine Gel	Dapivirine Placebo	Females	30	2x/day	112	Unclear	Rwanda, South Africa, Tanzania
Nel 2009 (IPM005B)	Dapivirine Gel	HEC Placebo Gel	Females	30	2x/day	36	Unclear	Belgium
Peterson 2007	SAVVY Gel	HEC* Placebo Gel	High Risk Females	22.7 (3.6)	1x before each vaginal intercourse	2142	Low	Ghana
Richardson 2000	Nonoxynol-9 Gel	Nonoxynol-9 Placebo	High Risk Females	28	1x before first vaginal intercourse of the day	278	Unclear	Kenya
Skoler-Karpoff 2008	Carraguard Gel	Methylcellulose Placebo Gel	Females	30.6	1 hr. before each vaginal intercourse	6202	Unclear	South Africa
Van Damme 1998	COL-1492 (nonoxynol-9) Gel	Nonoxynol-9 Placebo Gel	Females	31	1x/ day	375	Unclear	Netherlands, Belgium, Thailand
Van Damme 2002	COL-1492 (nonoxynol-9) Gel	Repels polycarbophil	High Risk Females	26	1x before each vaginal intercourse	892	Unclear	Benin, South Africa, Côte-d'Ivoire, Thailand
Van Damme 2008	Cellulose Sulphate Gel	Placebo Gel	Females	28	1x before each vaginal intercourse	1425	Unclear	Benin, India, South Africa, Uganda
*HEC = hydroxyethylcellulose gel; *RAI = receptive anal intercourse								

Figures

Figure 1

Modified PRISMA Flow Chart

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bunge 2018	●	?	?	●	●	?	?
Carraguard Team 2010	●	●	●	●	●	?	●
Delany-Moretlwe 2018	●	●	●	●	●	●	●
Doh 2007	●	●	●	?	●	?	●
Feldblum 2008	●	●	●	●	●	●	●
Halpern 2008	●	●	●	●	●	●	●
Hoffman 2004	●	●	●	●	●	●	●
Karim 2010	●	●	●	●	●	●	●
Karim 2011	●	●	●	●	●	●	●
Kilmarx 2006	●	●	●	●	●	?	●
Kilmarx 2008	●	●	●	●	?	?	●
Low-Beer 2002	?	●	●	●	●	?	●
Marrazzo 2015	●	●	●	●	●	●	●
Mbopi-Keou 2010	●	●	●	●	●	?	●
McCormack 2010	●	●	●	●	●	●	●
McGowan 2011	●	?	●	●	●	?	●
McGowan 2012	?	●	?	?	●	●	●
Nel 2009 (IPM003)	●	●	●	●	●	?	?
Nel 2009 (IPM005B)	●	●	●	●	●	?	?
Peterson 2007	●	●	●	●	●	●	●
Richardson 2000	●	●	●	●	●	?	●
Skoler-Karpoft 2008	●	●	●	●	●	?	●
Van Damme 1998	?	?	●	●	●	?	●
Van Damme 2002	●	?	●	●	●	?	●
Van Damme 2008	●	●	●	●	●	?	●

Figure 2

Risk of Bias Summary

Figure 3

Forest plot of HIV incidence