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REVIEW PAPER

Comparative efficacy of topical microbicides in the prevention of HIV transmission – results from a systematic review and network meta-analysis

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ABSTRACT

Introduction and aim. Preventing new HIV infections is crucial, particularly for women and girls at high risk. Vaginal microbicides offer a female-controlled HIV prevention method. This systematic review evaluated the comparative efficacy of topical microbicides in preventing HIV transmission.

Material and methods. Electronic databases were searched up to May 2024 for randomized controlled trials (RCTs) comparing topical microbicides versus placebo/no treatment in sexually active women. The primary outcome was the incidence of HIV. A random effects network meta-analysis (NMA) was employed. Relative ranking was assessed using surface under the cumulative ranking curve (SUCRA) probabilities.

Analysis of literature. Thirteen RCTs were included in the review comparing the dapivirine ring, the tenofovir gel, BufferGel, PRO 2000, Carraguard, cellulose sulfate, or SAVVY against placebos. Compared to placebo, only dapivirine significantly reduced HIV incidence (risk ratio (RR) 0.71 [95% CI 0.56 to 0.91]). Dapivirine was superior to BufferGel (RR 0.61 [95% CI 0.39 to 0.94]) and SAVVY (RR 0.52 [95% CI 0.28 to 0.97]). Dapivirine ranked highest in efficacy (SUCRA=0.93), followed by tenofovir (SUCRA=0.76). In general, consistent network results with some small study effects.

Conclusion. This study supports the use of the vaginal dapivirine ring for HIV prevention over SAVVY or BufferGel. More high-quality trials are needed to validate the efficacy of tenofovir gel.

Keywords. HIV, topical microbicides, vaginal microbicides

Introduction

Human immunodeficiency virus (HIV) infections remain a global health challenge, particularly in regions with high prevalence rates and limited access to prevention and treatment interventions. In 2022, approximately 39 million people lived with HIV, with 1.3 million new infections and 630,000 reported deaths reported. Of particular concern, in 2022, globally, 46% of all new HIV infections occurred among women and girls, with approximately 4,000 adolescent girls and young women aged 15–24 years who became infected with HIV every week.[1]

To control the HIV epidemic, the prevention of new infections is of crucial importance. Although preexposure

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prophylaxis (PrEP) is an effective option, it requires strict daily adherence to oral medications.[2] Another approach, male-controlled prevention methods, such as condoms and circumcision, offer limited power to women in managing their own exposure to HIV infection. Other prevention methods, such as postexposure prophylaxis and behavioral changes, also exist, but preventing HIV transmission remains a major public health challenge, particularly with respect to sexually active women.

Microbicides are defined by the World Health Organization (WHO) as "compounds that can be applied inside the vagina or rectum to protect against sexually transmitted infections (STIs), including HIV".[3] Vaginal microbicides, in particular, represent a female-controlled approach to prevent HIV, especially in situations where women are unwilling or unable to negotiate condom use. Microbicides would empower women to protect themselves, because they are a potential preventive option that they can easily control themselves and, most importantly, do not require the cooperation, consent, or even knowledge of the partner. Various topical microbicide formulations are available and the field is advancing with recent developments, particularly the role of nanotechnology, specifically dendrimers, in new formulations, which have shown promise in preclinical studies.[4,5]

In terms of clinical studies, numerous randomized controlled trials (RCTs)[6] have been conducted to evaluate the efficacy and safety of a variety of topical microbicide formulations including surfactants (SAVVY, nonoxynol-9), vaginal defense enhancers (BufferGel), entry inhibitors (Carragurard and PRO 2000) and antiretroviral drugs (tenofovir gel, dapavirine ring). In 2021, a Cochrane systematic review was published on the efficacy of topical microbicides in preventing sexually transmitted infections. The review included 12 trials with 32,464 participants.[6] The trials evaluated a wide range of compounds and delivery mechanisms, including gels, creams and intravaginal rings, each with its unique pharmacokinetic and pharmacodynamic properties. In the review, dapivirine demonstrated potential to prevent HIV, while other microbicides had limited success. Dapivirine may be particularly attractive due to its use in slow-release devices, which are effective for longer durations compared to vaginal gels and creams that must be applied before and/or after each sexual encounter.[7] Overall, while some of the trials produced encouraging results, others were inconclusive or even contradictory, resulting in a fragmented evidence base that hinders the identification of optimal microbicide candidates to be recommended for widespread distribution and use.

Aim

A major challenge in synthesizing evidence from existing RCTs is the lack of head-to-head comparisons of different microbicide formulations. Typically, trials evaluate a single candidate microbicide against a placebo, making it difficult to compare the relative effectiveness of different interventions. Consequently, there is a pressing need in this situation to use a comprehensive comparative analysis method that integrates data from multiple trials and allows indirect comparisons, thereby ranking available treatment options based on their efficacy. In this systematic review and network meta-analysis, our aim was to comprehensively evaluate the efficacy of available topical microbicides in preventing HIV transmission.

Material and methods

The protocol for this study was registered with Open Science Framework (https://osf.io/5fknw). This review followed the PRISMA extension statement for systematic reviews that incorporate network meta-analyses.[8]

Search strategy and study selection

We identified relevant studies by systematic search of PubMed, EMBASE, and the Cochrane CENTRAL Register of Controlled Trials from January 2020 to the 7th of May 7, 2024. The search was restricted to studies published from 2020 onward because studies published up to 2019 could be identified from previously published systematic reviews.[6] In addition, we manually checked the reference lists of published systematic reviews. In this study, we did not consider conference abstracts. The general search strategy is provided in Appendix S1. Two reviewers (E.L. and K.K.) independently performed screening of titles and abstracts for relevance and then selected the studies for inclusion after examining the full text of the potentially eligible articles. Any discrepancies were resolved by discussion with a third reviewer (S.V.). We included randomized controlled trials (RCTs), which followed participants for at least 12 months and compared the use of topical microbicides including detergent-like products (surfactants), vaginal defense enhancers, entry inhibitors, and antiretroviral drugs with placebo or without treatment. Eligible participants were sexually active nonpregnant heterosexual women (i.e. women who have sex with men), 16 years and above in any setting, who had no laboratory-confirmed HIV at baseline. Studies investigating nonoxynol-9 were excluded from the review because current evidence from a WHO report indicates that nonoxynol-9-containing spermicides do not protect against HIV infection and may even increase the risk of HIV infection in women who use these products frequently.[9] The outcome of interest in this review was laboratory-confirmed incidence of HIV. We excluded quasirandomized trials because such studies produce effect sizes that indicate more extreme benefits when compared with randomized trials.[10]

Data extraction and quality assessment

Data extraction was performed independently by two reviewers (EL and N.N.) using standard data extraction

forms. For the result, we used the initial number of participants randomized to each trial arm and performed the analyzes regardless of how the authors of the original trials had analyzed the data (intention-to-treat principle).[10] Two reviewers (EL and S.S.) independently assessed the risk of bias within each study using the Cochrane Risk of Bias tool.[11] The tool covers the following domains: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. Each domain was assessed and categorized into low, high, or unclear risk of bias. Discrepancies were resolved by consensus. Each study will be classified with an summary risk of bias assessment according to Cochrane's criteria:[11] "low risk of bias" if the study is assessed as low risk across all key domains; "unclear risk of bias" if the study is assessed with low or unclear risk across all key domains; and "high risk of bias" if the study is assessed with a high risk of bias in one or more key domains.

Data synthesis and statistical analysis

The outcome measure was estimated as the risk ratio (RR), which is the ratio between the incidences of HIV in the intervention arm and those in the control arm along with a 95% confidence interval (CI). For direct comparisons, we performed standard pairwise meta-analyses using the DerSimonian and Laird random effects model to estimate the pooled effect size.[12] If a direct comparison was based on two or more trials, we assessed heterogeneity between trials using I^2 statistics. We used a random-effects NMA using a consistency model within a frequentist approach to incorporate indirect evidence with direct evidence.[13] 'Control or placebo' was used as a common comparator in the network model. The inconsistency assumption was evaluated using the global inconsistency test by fitting design-by-treatment into the inconsistency model.[13] The network inconsistency assumption, which refers to a disagreement between direct and indirect estimates, was evaluated using the loop-specific approach.[14] We used surface under the cumulative ranking curve (SUCRA), which estimates the probabilities for all treatments to obtain a treatment ranking based on efficacy.[15] Higher SUCRA scores (ranging from 0 to 1) indicated that the intervention has a high likelihood of being best. We examined the effects of the small study using a comparison adjusted for comparison.[13] To assess the robustness of our findings, we performed sensitivity analyzes excluding small-sized (<25th percentiles) trials[16] and high risk bias trials. For statistical analysis, we used Stata version 16.0 (StataCorp, College Station, TX, USA). We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, adapted to network meta-analysis, to rate the quality of evidence.

Analysis of the literature

The database search resulted in 1440 records. After eliminating 15 duplicates, 1425 titles and abstracts were selected based on the predefined eligibility criteria. Subsequently, 16 records underwent further screening, but all were excluded because they did not assess HIV incidence as an outcome or investigated oral pre-exposure prophylaxis medications only. Consequently, the 13 studies incorporated into this network meta-analysis were those previously included in other systematic reviews (Fig. 1).

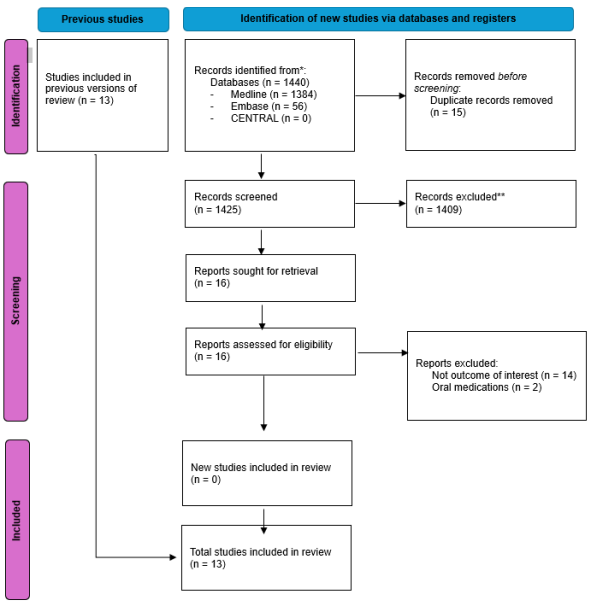


Fig. 1. PRISMA flow diagram

Characteristics of studies

The characteristics of the 13 included studies are summarized in Table 1. All 13 trials were parallel RCTs conducted in sub-Saharan Africa, one study also having a site in the USA and another in India.[7,17-28] The vaginal microbicides tested included BufferGel and PRO 2000 (1 trial, 3101 women), Carraguard (2 trials, 6602 women), cellulose sulfate (2 trials, 3069 women), C31G (SAVVY) (2 trials, 4295 women), dapivirine ring (2 trials, 4588 women), PRO 2000 (1 trial, 9385 women), and tenofovir gel (3 trials, 4958 women).[17,18,25-28] All microbicides were compared to placebo in these RCTs.

Two trials used vaginal rings,[7,20] while the others used vaginal gels. In the ring trials, women in the intervention group used vaginal rings containing 25 mg of dapivirine, worn continuously for a month, and replaced at each monthly follow-up visit. In two trials,[25,26] women used 1% tenofovir gel, inserting one dose within 12 hours before and another after vaginal sex, with a maximum of two doses over a 24-hour period. In the third study,[22] the tenofovir gel was inserted up to one hour before intercourse. The gels were supplied in prefilled single-use applicators. For the five other types of vaginal microbicide gels (cel-

lulose sulfate, SAVVY, PRO 2000, BufferGel, and Carraguard), women were instructed to insert the gel within an hour before vaginal intercourse. All of those gels were provided in pre-filled single-use applicators.

Figures 2 and 3 show the risk of bias assessment for each included study. Most of the studies were rated as overall low risk of bias. The two studies rated as overall high risk of bias were due to incomplete outcome data.

Fig. 2. Risk of bias assessment for each included study

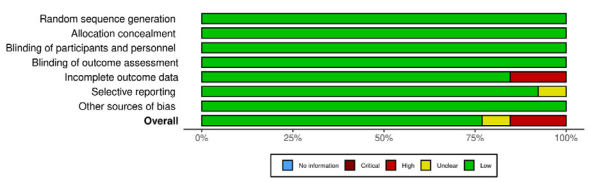


Fig. 3. Summary of the risk of bias assessment for included studies

Network meta-analysis findings: HIV incidence

All 13 RCTs provided dichotomous data for HIV incidence. The resulting network plot is provided in Figure 4. The network meta-analysis suggested that, compared to placebo, dapivirine (RR, 0.71 [95%CI, 0.56 to 0.91]) statistically significantly reduces the risk of acquiring HIV infection (Fig. 5). The other microbicides, when compared with placebo, appear to result in little to no difference in the risk of acquiring HIV. In this category were tenofovir (RR 0.83, [95% CI 0.66, 1.03]), Carraguard (RR, 0.89 [95% CI 0.68,1.16]), PRO 2000 (RR, 0.92 [95%CI, 0.71,1.19]), BufferGel (RR, 1.17 [95%CI, 0.81,1.70]), cellulose sulphate (RR, 1.20 [95%CI, 0.72,1.99]), and SAVVY (RR, 1.37 [95%CI, 0.77, 2.44]) (Fig. 5). These findings are similar to those obtained using standard pairwise meta-analyzes (Fig. 5 and 6).

Table 1. Summary of characteristics of included studies

ID	Author, year	Country	Age	Intervention	Comparator	Trial discontinued
1	Abdool Karim, 2010	South Africa	18 to 40 years	Tenofovir 1% gel and condom	Placebo gel and condom	No
2	Abdool Karim, 2011	Malawi, South Africa, Zambia, Zimbabwe, and USA	18 years and older	1. BufferGel 2. 0.5% PRO 2000	1. Placebo gel 2. No gel	No
3	Baeten, 2016	Malawi, South Africa, Uganda, and Zimbabwe	18 to 45 years	Dapivirine 25mg vaginal ring	Placebo vaginal ring	No
4	Delany-Moretlwe, 2018	South Africa	18 to 30 years	Tenofovir 1% gel	Placebo gel	No
5	Feldblum, 2008	Nigeria	18 to 35 years	C31G (SAVVY) 1.0% gel and condom	Placebo gel	Yes
6	Halpern, 2008	Nigeria	18 to 35 years	Cellulose sulphate and condom	Placebo gel and condom	Yes
7	Marrazzo, 2015	South Africa, Uganda, Zimbabwe	18 to 45 years	Tenofovir 1% gel	Placebo gel	Yes
8	McCormack, 2010	South Africa, Uganda, Zambia, and Tanzania	18 years or older, (> 16 years in Tanzania and Uganda)	1. PRO 2000 2% gel and condom2. PRO 2000 0.5% gel and condom	Placebo gel and condom	Yes – 2% gel
9	Nel, 2016	South Africa, Uganda	18 to 45 years	Dapivirine 25mg vaginal ring	Placebo	No
10	Peterson, 2007	Ghana	18 to 35 years	C31G (SAVVY) 1% and condom	Placebo and condom	Yes
11	Skoler-Karpoff, 2008	South Africa	16 years and older	Carraguard gel and condom	Placebo gel and condom	No
12	Van Damme, 2008	South Africa, Uganda, Benin, and India	18 years and older	Cellulose sulphate 6% gel and condom	Placebo gel and condom	Yes
13	Carraguard, Phase II South Africa Team 2010	South Africa	18 years and older	Carraguard	Placebo	No

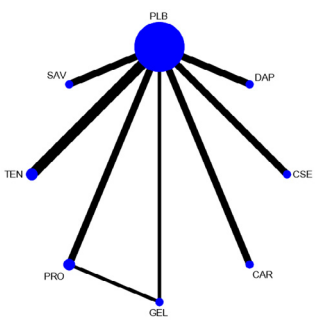


Fig. 4. Network plot, notes: The size of the nodes corresponds to the number of trials that study the treatments. Directly comparable treatments are linked with a line; The thickness of the line corresponds to the number of trials that assess the comparison, DAP dapavirine, CAR – carraguard, CSE cellulose sulphate, GEL – BufferGel, PLB placebo, PRO – PRO 2000, SAV SAVVY, TEN – tenofovir

When we evaluated comparative efficacy among different microbicides, dapivirine was superior in reducing the risk of HIV infection compared to BufferGel (RR, 0.61 [95%CI, 0.39, 0.94]) and SAVVY (RR, 0.52 [95%CI, 0.28, 0.97]) (Fig. 4). No statistically significant differences were observed between other interventions. The SUCRA plot revealed that dapivirine (SUCRA=0.93) was ranked first for efficacy followed by tenofovir (SUCRA=0.76), Carraguard (SUCRA=0.64), PRO 2000 (SUCRA=0.60), BufferGel (SUCRA=0.25), cellulose sulfate (SUCRA = 0.25) and SAVVY (SUCRA=0.15) (Fig. 7).

CAR	NA	NA	NA	NA	NA	NA	0.89 (0.79,1.11)
0.75 (0.42,1.32)	**CSE**	NA	NA	NA	NA	NA	1.15 (0.59,2.25)
1.25 (0.87,1.80)	1.68 (0.96,2.95)	**DAP**	NA	NA	NA	NA	0.71 (0.57,0.89)
0.76 (0.48,1.20)	1.02 (0.54,1.90)	0.61 (0.39,0.94)	**GEL**	1.49 (0.99,2.22)	NA	NA	1.05 (0.73,1.52)
0.97 (0.67,1.41)	1.30 (0.74,2.29)	0.78 (0.54,1.11)	1.28 (0.87,1.89)	**PRO**	NA	NA	0.88 (0.63,1.25)
0.65 (0.34,1.23)	0.87 (0.40,1.88)	0.52 (0.28,0.97)	0.86 (0.43,1.70)	0.67 (0.36,1.26)	**SAV**	NA	1.35 (0.70,2.58)
1.08 (0.76,1.53)	1.45 (0.83,2.51)	0.86 (0.62,1.20)	1.42 (0.92,2.19)	1.11 (0.79,1.55)	1.66 (0.89,3.08)	**TEN**	0.82 (0.65,1.05)
0.89 (0.68,1.16)	1.20 (0.72,1.99)	0.71 (0.56,0.91)	1.17 (0.81,1.70)	0.92 (0.71,1.19)	1.37 (0.77,2.44)	0.83 (0.66,1.03)	**PLB**

Fig. 5. Pairwise (upper right portion) and network (lower left portion) meta-analytic results for HIV incidence, notes: results are expressed as risk ratios (95% CI). For pairwise meta-analyses, RR <1 indicates that the treatment specified in the row is more effective. For the NMA, RR <1 indicates that the treatment specified in the column is more effective. Green shaded results indicate statistical significance, DAP dapavirine, CAR – carraguard, CSE cellulose sulphate, GEL – BufferGel, PLB placebo, PRO – PRO 2000, SAV SAVVY, TEN – tenofovir

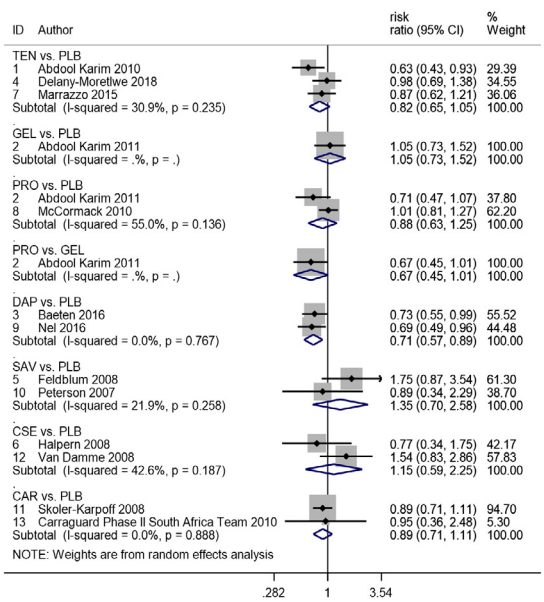


Fig. 6. Results of the meta-analysis of the pairwise analysis, DAP dapavirine, CAR – carraguard, CSE cellulose sulphate, GEL – BufferGel, PLB placebo, PRO – PRO 2000, SAV SAVVY, TEN – tenofovir

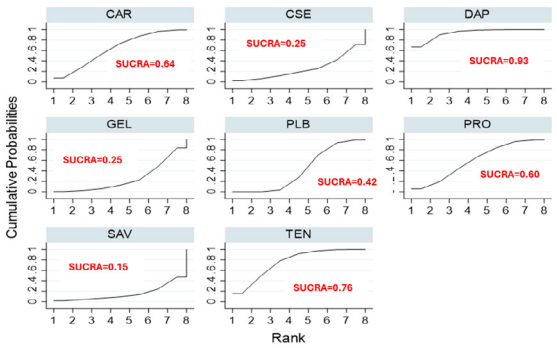


Fig. 7. SUCRA ranking of efficacy, DAP – dapavirine, CAR carraguard, CSE – cellulose sulfate, GEL – BufferGel, PLB – placebo, PRO PRO 2000, SAV – SAVVY, TEN – tenofovir

Network consistency and small study effects

The global inconsistency using the 'design-by-treatment' interaction model and the loop-specific approach did not demonstrate evidence of inconsistency (Fig. 8). The comparison-adjusted funnel plot demonstrated some evidence of small study effects (Fig. 9).

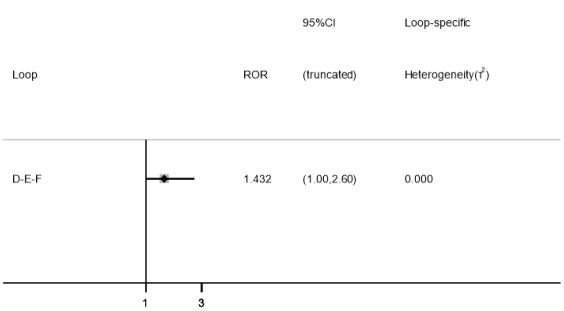
Test of global inconsistency

```
Testing for inconsistency:
 ( 1)  [_y_F]des_EF = 0

           chi2(  1) =    2.22
         Prob > chi2 =    0.1360
```

Note: Global inconsistency in a network can be evaluated and detected using inconsistency models. These models differ from the consistency models by relaxing the consistency equations and allowing intervention effects to vary when estimated directly and indirectly. A p-value less than 0.05 indicates the presence of inconsistency.

Loop-specific approach



Note: The loop-specific approach considers only triangular and quadratic loops. In this case, only one triangular loop is formed (Gel-PRO-PLB) as in Figure 1 (network plot). The plot shows that only one triangular loop is formed and there is no statistically significant inconsistency as the confidence intervals for RoRs are compatible with zero inconsistency (RoR is close to 1)

Fig. 8. Inconsistency testing

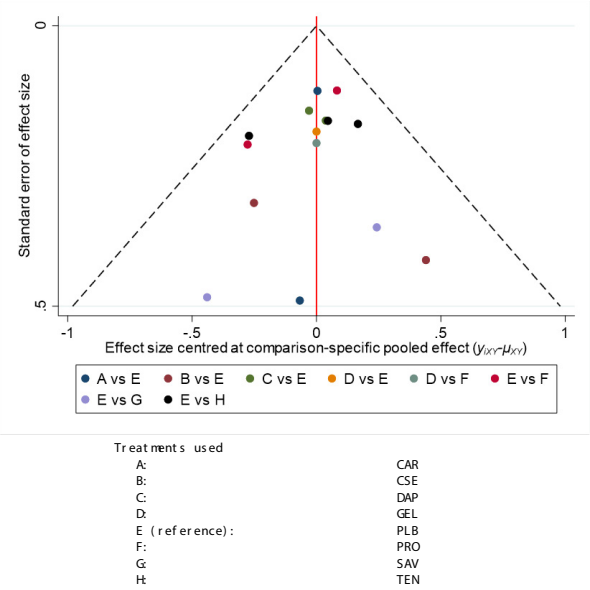


Fig. 9. Comparison-adjusted funnel plot, DAP dapavirine, CAR – carraguard, CSE cellulose sulphate, GEL – BufferGel, PLB placebo, PRO – PRO 2000, SAV SAVVY, TEN – tenofovir

Sensitivity analysis and GRADE summary of evidence

The results were not affected by the sensitivity analyzes based on excluding small-sized studies and trials of high risk of bias (Table 2). Overall, the quality of evidence based on the application of GRADE criteria to the findings of the NMA was generally rated as very low to moderate quality (Table 3). We had moderate confidence in estimates supporting the use of vaginal dapivirine compared to placebo in terms of reducing the risk of HIV acquisition.

Table 2. Sensitivity Analyses for primary outcome*

Comparison	Primary	Excluding high ROB trials	Excluding small sized studies
		Risk ratio (95% CI)	
CAR vs PLB	0.89 (0.68, 1.16)	0.89 (0.69, 1.15)	0.88 (0.67, 1.19)
CSE vs PLB	1.20 (0.72, 1.99)	1.54 (0.82, 2.90)	1.30 (0.62, 2.11)
DAP vs PLB	0.71 (0.56, 0.91)	0.71 (0.56, 0.90)	0.71 (0.53, 0.94)
GEL vs PLB	1.17 (0.81, 1.70)	1.18 (0.82, 1.69)	1.13 (0.80, 1.75)
PRO vs PLB	0.92 (0.71, 1.19)	0.92 (0.71, 1.19)	0.90 (0.68, 1.30)
SAV vs PLB	1.37 (0.77, 2.44)	0.89 (0.34, 2.30)	1.32 (0.67, 2.98)
TEN vs PLB	0.83 (0.66, 1.03)	0.83 (0.67, 1.03)	0.80 (0.61, 1.34)

* DAP dapavirine, CAR – carraguard, CSE cellulose sulphate, GEL – BufferGel, PLB placebo, PRO – PRO 2000, SAV SAVVY, TEN – tenofovir

The GRADE approach adapted to network meta-analysis was used to rate the quality of evidence into four levels: high, moderate, low, and very low quality. In this approach, direct estimates from RCTs rated at high quality and can be graded down to moderate, low, and very low quality based on risk of bias, indirectness, imprecision, inconsistency, and publication bias. The rating of the quality of the indirect estimates starts at the lowest rating of the two direct estimates that contribute to the indirect estimate of the comparison of interest as first-order loops. In the presence of intransitivity, indirect estimate can be further rate down from the lower of the confidence ratings of the contributing direct comparisons. Finally, if both direct and indirect evidence is available, then the higher of the two quality ratings can be assigned to the quality rating for NMA estimates.

Table 3. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Summary of evidence*

Comparisons	Direct evidence (from pairwise meta-analysis)		Indirect evidence (from node-splitting)		Network meta-analysis	
Partial/ complete resolution	RR [95% CI]	Quality of evidence	RR [95% CI]	Quality of evidence	RR [95% CI]	Quality of evidence
CAR vs PLB	0.89 (0.79, 1.11)	Low	NA	NA	0.89 (0.68, 1.16)	Low
CSE vs PLB	1.15 (0.59, 2.25)	Very low	NA	NA	1.20 (0.72, 1.99)	Very low
DAP vs PLB	0.71 (0.57, 0.89)	Moderate	NA	NA	0.71 (0.56, 0.91)	Moderate
GEL vs PLB	1.05 (0.73, 1.52)	Low	-0.7705791 (SE 0.4411362)#	Very low	1.17 (0.81, 1.70)	Very low
PRO vs PLB	0.88 (0.63, 1.25)	Low	NA	NA	0.92 (0.71, 1.19)	Low
SAV vs PLB	1.35 (0.70, 2.58)	Very low	NA	NA	1.37 (0.77, 2.44)	Very low
TEN vs PLB	0.82 (0.65, 1.05)	Low	NA	NA	0.83 (0.66, 1.03)	Low
DAP vs GEL	NA	NA	0.61 (0.39, 0.94)	Low	0.61 (0.39, 0.94)	Low
DAP vs SAV	NA	NA	0.52 (0.28, 0.97)	Low	0.52 (0.28, 0.97)	Low
DAP vs TEN	NA	NA	0.86 (0.62, 1.20)	Low	0.86 (0.62, 1.20)	Low

Randomized controlled trials (RCTs) without important limitations are rated high on the GRADE scale. However, the above results are from long-term observational follow-up of RCTs with proper random sequence generation during the intervention phase. Hence, the initial quality rating starts with moderate level.
a. risk of bias
b. imprecision
c. Imprecision (close to null effect)
d. Based on rating of the two pairwise estimates that contribute to the indirect estimate (first-order loop)
e. Inconsistency
f. Intransitivity
g. Indirectness

* DAP dapavirine, CAR – carraguard, CSE cellulose sulphate, GEL – BufferGel, PLB placebo, PRO – PRO 2000, SAV SAVVY, TEN – tenofovir, # – log form

Discussion

This systematic review and network meta-analysis evaluated the efficacy of available topical microbicides in preventing HIV transmission. Despite our search for new RCTs from 2020 to 2024, no new studies were identified. The absence of recent publications may be attributed to several factors. There have been no significant breakthroughs in the development of widely available topical microbicides for HIV prevention, and challenges related to efficacy, safety, and user acceptability continue to impede their broad adoption.[29,30] Furthermore, recent research trends, as highlighted in the AIDS 2024 Research Roundup,[31] highlighted a focus toward long-acting injectable PrEP rather than topical microbicides. However, it is crucial to recognize that the field is evolving. For example, a safety study for a vaginal ring containing dapivirine and levonorgestrel is currently underway,[32] and several preclinical studies are investigating various combinations of antiretroviral drugs (eg, dapivirine, islatravir) with hormonal contraceptives (e.g., ethinylestradiol, etonogestrel) that demonstrated potential.[30] There may also be ongoing clinical trials or preclinical studies not yet widely published. Further exploration and continued monitoring of emerging studies are essential to understanding the future direction of research in this area.

Conventional meta-analysis has previously indicated that the vaginal dapivirine ring may be an effective intervention for preventing HIV.[6,33] Other interventions such as tenofovir, carraguard, cellulose sulfate, BufferGel, PRO 2000 and SAVVY have also been tested for this purpose. But in the absence of adequate head-to-head trials, their relative efficacy remains unclear. Conventional pairwise meta-analyzes offer only limited information because they compare interventions in pairs and do not use all available data to inform decision-making optimally. In contrast, NMA combines direct and indirect evidence from a network of RCTs to compare the efficacy of all available interventions. Thus, NMA improves the precision of the efficacy estimates, even if there are no direct comparisons. This is the first systematic review with NMA to assess the comparative effectiveness of topical microbicides for HIV prevention.

Overall, the findings of this NMA revealed that dapivirine ranks first for efficacy and was the only statistically significant intervention compared to placebo in preventing HIV. This aligns with the findings of a Cochrane systematic review, which indicated that dapivirine probably reduces the risk of developing HIV infection, while other topical microbicides may result in little or no difference in the risk of acquiring HIV.[6] Additionally, this NMA contributes strong evidence that dapivirine is statistically significantly more effective than SAVVY and BufferGel.

The only current licensed pharmaceutical HIV prevention methods are injectables or daily oral pills for PrEP.[2,34] While these PrEP methods are safe and effective when used as prescribed, maintaining a daily pill regimen or receiving regular injections can be challenging for some people. Consequently, other forms of HIV prevention, such as microbicides, are being developed and studied. Microbicides may offer specific advantages for some women, as they can be used without requiring negotiation with a sexual partner, making them preferable to condoms for HIV prevention. Given the high risk of HIV for women and girls in many regions,[1] it is crucial to have an effective, appealing, women-initiated HIV prevention method. Almost half of the global population living with HIV is women, who primarily contract the virus through heterosexual contact.[35,36] Evidence, including findings from this NMA and previous systematic reviews,[6,33] suggests that the vaginal dapivirine ring likely reduces the risk of HIV acquisition in heterosexual women.

One main issue with topical microbicides is adherence. The dapivirine ring, which is longer-acting and only needs to be left in place for a month, has potential advantages over coitally dependent or daily-use products. However, data from the two dapivirine trialsindicated poor adherence of the rings, as measured by residual amounts of dapivirine in those rings.[37,38] Reports of non-adherence included removing the rings for sex, bathing, in menses or extended periods, and reinserting them shortly before clinic visits. Reasons reported for non-adherence included hygiene concerns, external influences, and interest solely in study benefits, with some women removing the ring to get pregnant or use other vaginal products. Despite these challenges, two expanded open-label trials involving HIV-negative women who had participated in previous phase 3 trials demonstrated that the dapivirine ring is acceptable. These trials reported a reduction in the risk of HIV seroconversion under conditions closer to real-world settings, with less frequent clinic visits and HIV tests than the more rigorously controlled RCTs.[37] These findings support the probability that improved adherence will occur once women are aware of the ring's efficacy and safety of the ring and, in turn, suggest that the dapivirine ring is a feasible and acceptable HIV prevention method for women.

In 2020, the European Medicines Agency issued a positive scientific opinion on the monthly dapivirine vaginal ring.[39] Subsequently, the WHO recommended the ring as part of combination prevention strategies for women at high risk of acquiring HIV.[40] The dapivirine ring has been approved in Zimbabwe and several other countries in eastern and southern Africa, with additional approvals pending.[41] If further approved by national regulatory agencies, the monthly dapivirine ring would offer women a discreet and long-acting HIV prevention option that they can control, enhancing its potential as

a vital tool in reducing HIV transmission among women worldwide. Another key consideration is the economic implications, as cost-effectiveness studies for the dapivirine ring are currently limited.[42,43] More research is needed to evaluate its cost-effectiveness in different settings, considering factors such as user demand and adherence.

In this NMA, tenofovir ranked second but was not statistically significant. The comparative efficacy of dapivirine and tenofovir is also not statistically significant. The direction of effect indicates a beneficial effect of tenofovir in preventing HIV, although this finding did not achieve statistical significance. As such, additional high-quality clinical trials are needed to further evaluate the effectiveness of tenofovir.

Study limitations

This review is the first to integrate data from multiple trials into a network meta-analysis to evaluate the efficacy of topical microbicides in preventing HIV transmission. However, several limitations must be acknowledged. Our search strategy was limited to English-language publications only, thereby excluding relevant studies published in other languages. Findings should be interpreted with caution due to heterogeneity between studies, which arises from variations in microbicide formulations, study locations, sample sizes, and follow-up durations. Most of the trials were conducted in low and middle-income countries, primarily in Africa, with varying durations of follow-up. Given the lower incidence of HIV among women in high-income countries, studies assessing the effectiveness of these interventions may be predominantly limited to sites in low-income countries. Thus, the generalizability of the findings in various countries or regions with diverse socioculturral contexts is limited. The most promising interventions to prevent HIV infection were dapivirine and tenofovir, respectively, both exclusively tested in African trial sites. However, the limited sample size and number of studies may restrict the broad applicability of these findings. Furthermore, there is a potential for publication bias, with some evidence suggesting small study effects.

Conclusion

In conclusion, the findings of this review support the use of the dapivirine vaginal ring for the prevention of HIV, demonstrating its superiority over SAVVY and BufferGel. Integration of dapivirine into comprehensive HIV prevention programs holds promise for significantly reducing HIV transmission rates, particularly in regions where women face disproportionate risks. Although tenofovir gel shows promise, more research and high-quality clinical trials are necessary to confirm its efficacy.

Supplementary materials

S1: Search Strategy

Declarations

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Author contributions

Conceptualization, E.L. and S.V.; Methodology, E.L. and S.V.; Formal Analysis, E.L. and S.V.; Investigation, E.L., S.S., S.K., N.N., and S.V.; Data Curation, S.V.; Writing – Original Draft Preparation, E.L., F.S., and S.V.; Writing – Review & Editing, E.L., S.S., S.K., F.S., N.N. and S.V.; Visualization, S.V.; Project Administration, E.L.

Conflicts of interest

The authors have no competing interests to declare thatare relevant to the content of this article.

Data availability

All data relevant to the review are included in this published article and its supplementary information files. In this review, no new data was generated in this review, as it is based on previously published randomized controlled trials.

Ethics approval

Not applicable.

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