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Grant Murewanhema (✉ gmurewanhema@yahoo.com)

University of Zimbabwe

Moffat Malisheni

Ministry of Health, Zambia

Noah Fongwen Takah

Limbe Regional Hospital, Ministry of Public Health, Cameroon

Research article

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Posted Date: May 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-65554/v1>

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The effectiveness of tenofovir-based pre-exposure prophylaxis for prevention of HIV acquisition among Sub-Saharan African women at high risk: a systematic review

Grant Murewanhema¹, Moffat Malisheni², Noah Fongwen Takah^{3,4}

1. Department of Obstetrics and Gynaecology, College of Health Sciences, University of Zimbabwe, PO Box A178, Avondale, Harare, Zimbabwe
2. Ministry of Health, Zambia
3. Limbe Regional Hospital, Ministry of Public Health, Cameroon
4. International Diagnostics Centre Africa, Addis Ababa, Ethiopia

Corresponding Author: Grant Murewanhema (MB.ChB., MPH); gmurewanhema@yahoo.com; +263774430144. Department of Obstetrics and Gynaecology, University of Zimbabwe College of Health Sciences, PO Box A178, Avondale, Harare, Zimbabwe

Abstract

Background

Women in Sub-Saharan Africa (SSA) are disproportionately affected by the HIV epidemic. In 2019, they constituted 59% of new infections; thus, they remain a key population for control. Public health interventions to prevent acquisition of HIV in this high-risk population are urgently needed. Tenofovir-based pre-exposure prophylaxis (TFV-PrEP) has been shown to reduce HIV infections in other key populations. However, comprehensive evidence regarding TFV-PrEP effectiveness in women living in SSA has not been determined. Therefore, we undertook a systematic review to determine the effectiveness of tenofovir-1% (TFV-1%) vaginal gel, oral tenofovir (TFV) and tenofovir-emtricitabine (TDF-FTC) pre-exposure prophylaxis for primary acquisition of HIV in at-risk women living in SSA.

Methods

OVID MEDLINE, EMBASE, CENTRAL, Web of Science and Clinical Trials.gov were searched for eligible studies from 01 January 2020 to 31 July 2020. Only randomised controlled trials (RCTs) conducted in women living in SSA were included. Measures of effectiveness (hazard ratios (HR), incidence rate ratios (IRR)) were extracted from individual studies to determine the effectiveness of TFV-PrEP in preventing HIV infection among at-risk women living in SSA.

Results

From 2002 non-duplicate articles, four RCTs evaluating the effectiveness of one or more of the interventions against placebos were included. TFV-1% vaginal gel, oral TDF or TDF-FTC were not effective in preventing the acquisition of HIV infection in women living in SSA. However, poor adherence by study participants could have confounded the true effectiveness of TFV-PrEP in this high risk population. Meta-analysis was not conducted given the limited number of eligible studies identified from the search.

Conclusion

The current evidence does not support the effectiveness of TFV-PrEP for HIV in SSA women. More studies aimed at addressing factors driving low adherence to HIV interventions in this high risk population are urgently needed in order to improve the design of future RCTs leading to the determination of more reliable estimates of TFV-1% vaginal gel or oral TDF or TDF-FTC effectiveness.

Protocol registration: This systematic review was not registered in PROSPERO.

Keywords: HIV, Sub-Saharan African Women, Pre-Exposure Prophylaxis, Tenofovir 1% vaginal gel, oral tenofovir, Truvada, effectiveness

Background

Recent UNAIDS estimates show that in Sub-Saharan Africa (SSA), women and girls constituted an estimated 59% of new HIV infections in 2019(1). Despite a marked reduction in incident HIV infections by 40% since the peak in 1998, SSA women remain at substantial risk of acquiring HIV(1). Young women remain a driving factor for the HIV epidemic and are a key population for control(2,3).

Pre-exposure prophylaxis (PrEP) refers to use of antiretroviral drugs by an individual at risk of HIV acquisition to prevent infection before the exposure occurs. The World Health Organisation (WHO) has included oral tenofovir-containing drugs for use as PrEP in groups at substantial risk of HIV acquisition(4). Efficacy of tenofovir-based pre-exposure prophylaxis (TFV-PrEP) was demonstrated in studies among men who have sex with men (MSM) and transgender women (TGW), with a 44% reduction (95% CI 15-63%, $p=0.005$) in HIV incidence attributable to Truvada (TDF-FTC)(5).

Women in the patriarchal African society usually have little or no control over the preventive methods available(6), and the search for effective pharmacological interventions continues to complement behavioural interventions(7). Based on results from studies conducted in MSM and TGW(8,9), TFV-PrEP offers a viable alternative of control for women at high-risk of HIV acquisition. However, comprehensive evidence regarding TFV-PrEP effectiveness in women living in SSA has not been determined. We

undertook a systematic review to determine the effectiveness of TFV-PrEP for prevention of acquiring HIV among at high-risk women residing in SSA.

Methods

Protocol and registration

This systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines(10,11) with additional guidance derived from the Cochrane Handbook of Systematic Reviews and Meta-analysis for Interventions(12). The protocol for this systematic review was not registered in PROSPERO.

Eligibility Criteria

The studies were restricted to heterosexual SSA women at risk of HIV acquisition. No limitation was placed on language. The interventions evaluated against their respective comparator placebos were TFV-1% vaginal gel, oral TDF and oral TDF-FTC. The outcome was effectiveness against HIV acquisition. Only Randomised Controlled Trials (RCTs) evaluating the effectiveness of the study products were included.

Information sources and search strategy

A systematic literature search in Medline, Embase, Web of Science, CENTRAL and ClinicalTrials.gov through OVID was conducted from 1 January 2020 to 31 July 2020. Multiple databases were searched to limit bias as recommended by the Cochrane Collaboration(12). The search strategies were constructed from combinations of Medical Subject Headings (MeSH) and keywords, which were adjusted for the individual databases by the Principal Investigator (GM) with inputs from MM and NFT. The Cochrane Highly Sensitive Strategy for identifying RCTs in Medline: sensitivity-maximising version (2008 revision); OVID format(12) was used to filter RCTs in Medline whilst the Scottish Intercollegiate Network search filters for RCTs(13) were utilised in Embase. No filters were applied in the remaining databases. Detailed search strategies in OVID Medline and Embase are shown in Appendix 1 and 2.

Results from each database were imported into Mendeley desktop version 1.19.4 and de-duplicated. GM, MM and NFT screened the titles and abstracts of the remaining studies for eligibility independently. All eligible studies were accessed except for the FACTS-001 study(14) for which only a conference abstract was found. All studies for which eligibility could not be determined based on the abstract were obtained in full for further assessment.

Data Collection Process and Data Items

A pre-tested data extraction sheet was developed in Microsoft Excel 2013 to facilitate data collection.

Study lead author, year of publication, geographical location, source of funding, journal of publication, number of participants and duration of follow-up were extracted. Age and reported measures of central tendency and spread were also extracted. Outcome specific headings used in the effectiveness review included effectiveness of each of TFV-1% vaginal gel, oral TDF and TDF-FTC. Odds ratios (OR), relative risk (RR), hazard ratios (HR) and incidence rate ratios (IRR) were extracted as summary measures.

Risk of Bias Assessments

The Cochrane Collaboration tool for assessing the risk of bias in RCTs was used(12,15). It is designed to identify selection, performance, attrition, detection, reporting and other biases.

Statistical Analysis

The results from the RCTs evaluating effectiveness of each of the study products against placebo were synthesized. We intended to conduct pairwise meta-analysis for each of TFV-1% vaginal gel, oral TDF and TDF-FTC against respective placebos in Stata version 11. Since the studies were conducted across different geographical locations and years, a source of significant heterogeneity, random effects meta-analyses were to be conducted, with fixed effects meta-analyses as sensitivity analyses. We obtained a limited number of studies and therefore we could not conduct meta-analysis, tests of heterogeneity and meta-regression. Heterogeneity was to be assessed using the I^2 . We could also not produce funnel plots to assess risk of publication bias owing to limited number of studies.

Results

Out of 2002 studies screened after removing duplicates, 70 full-text articles were assessed for eligibility, and four RCTs evaluating effectiveness of interventions and were included in synthesis for effectiveness. The study selection is detailed in the PRISMA flow diagram in Figure 1.

Characteristics of Included Studies

All studies were published in English, mostly between 2014 and 2015. They were conducted across centres in South Africa, Cameroon, Ghana, Nigeria, Uganda, Zimbabwe, Kenya and Tanzania. Gilead Sciences (TDF, TDF-FTC) and CONRAD (TFV-1% vaginal gel) provided the study products. Financial support was provided by the United States Agency for International Development (USAID), Family Health International 360 (FHI-360), the Centre for the AIDS Programme of Research in South Africa (CAPRISA), National Institutes for Health (NIH) and Bill and Melinda Gates Foundation. Peterson *et al* reported significant conflicts of

interests where individuals affiliated to sponsors were closely involved in study design, manuscript writing, revision, and decision to publish(16). All enrolled black SSA women, absolute ages 18-45 years with variations in the means/medians reported across the different studies. Adolescents below 18 years, who are also at risk, were excluded because of the need for parental/guardian consent.

The RCTs are fully characterised in table 1. All enrolled HIV-negative, non-pregnant, non-lactating women. HIV testing was performed in standard laboratories using standard kits to ensure uniformity of measurement and reduce misclassification bias. Study participants underwent monthly HIV testing, adherence measurement and risk-reduction counselling. Additionally, they were provided with standard HIV prevention packages. Karim *et al*(17), Peterson *et al*(16) and van Damme *et al*(18) evaluated the effectiveness of TFV-1% vaginal gel, oral TDF and TDF-FTC respectively against placebos in 1:1 randomisation ratios whilst Marrazzo *et al*(19) evaluated TFV-1% vaginal gel, oral TDF and TDF-FTC against placebos in a complex five-arm 1:1:1:1:1 trial. Effective randomisation was concluded by even distribution of baseline participant characteristics across all the studies; however, it was also notable that 62.8% of participants in the multi-national, multi-centre trial by Marrazzo *et al*(19) were from Durban sites. Karim *et al* reported differences with rural women being much younger, poorer and reported lower sexual frequency and condom use than their urban counterparts(17).

All studies followed the Consolidated Reporting of Trials (CONSORT) 2010 guidelines and included CONSORT flow diagrams accounting for study participants(20). Only Karim *et al*(17) and the TDF-FTC arm of Marrazzo *et al*(19) were able to follow-up participants for the originally planned follow-up period. The trial by van Damme *et al*(18) and the TFV-1% vaginal gel and oral TDF arms of the trial by Marrazzo *et al*(19) were stopped prematurely by Data Safety and Monitoring Bodies (DSMB) due to futility. The trial by Peterson *et al* was stopped prematurely in Nigeria due to poor protocol compliance and in Cameroon due to post-trial care of sero-converters(16).

Risk of bias assessment

Figure 2 shows the risk of bias across the four RCTs. Overall, the risk of bias was low; however, there were some sources of bias. Karim *et al*(17), Peterson *et al* and Marrazzo *et al*(19) adequately described or referred to the study protocol for details regarding sequence generation, allocation concealment and blinding whereas van Damme *et al*(18) did not. Thus, risk of bias was unclear for sequence generation and allocation concealment, and double-blinding was concluded from the abstract and text. Peterson *et al* selectively reported laboratory outcomes, excluding some from the Nigerian site(16). Participants were

not uniformly represented in all trials, with some sites overrepresented. However, due to effective randomisation noted this was probably inconsequential. Three of the studies(16,18,19) had all or part of them stopped prematurely, possibly failing to adequately power the studies.

Synthesis

The summary data for effectiveness of TFV-1% vaginal gel, oral TDF and TDF-FTC against their respective placebos are summarised in the table below. Owing to paucity of studies, we could not pool effect size estimates in meta-analyses, and we synthesized the evidence qualitatively. The summary data are shown in Table 2.

Karim *et al*(17) and Marrazzo *et al*(19) evaluated the effectiveness of TFV-1% vaginal gel. 2899 women contributing 3395.3 women-years of follow-up across the intervention and placebo arms. While Karim *et al* reported an adjusted 37% protective effect of the gel against HIV acquisition that was statistically significant(17), Marrazzo *et al* reported an insignificant 15% protective effect with a wide confidence interval(19). When stratified according to gel adherence by Karim *et al*(17), in high adherers (gel adherence > 80%), HIV incidence was 54% lower (P = 0.025) in the TFV-1% vaginal gel arm. In intermediate adherers (gel adherence 50 to 80%) and low adherers (gel adherence < 50%), the HIV incidence reduction was 38 and 28%, respectively(17). In a random sample in the study by Marrazzo *et al*, TFV was detected 25% of available plasma samples from participants assigned to TFV gel(19). Detection of TFV in plasma was negatively associated with characteristics predictive of HIV-1 acquisition(19).

Peterson *et al*(16) and Marrazzo *et al*(19) evaluated the effectiveness of oral TDF against placebo. 2592 women were enrolled in the two studies combined, contributing 2134.9 women years of follow-up. None observed statistically significant protection. Marrazzo *et al* terminated prematurely due to lack of effectiveness(19). The study by Peterson *et al* failed to reach the intended sample size and follow-up and thus was underpowered(16). Peterson *et al* did not provide HRs(16) whilst Marrazzo *et al* did not provide IRRs(19). Evaluation of effectiveness by Peterson *et al* was limited by the low number of endpoints observed(16). In a random sample, TFV was detected in 30% of available plasma samples from participants randomly assigned to receive TDF by Marrazzo *et al*(19). However, Peterson *et al* did not provide any measure of adherence(16).

Marrazzo *et al*(19) and van Damme *et al*(18) evaluated the effectiveness of oral TDF-FTC against oral placebo. 4112 women were enrolled across the arms in the two trials. No statistically significant protection was conferred. There was no notable clinical heterogeneity between the two studies. For all

the interventions, only 2 studies were obtained, each from the 5-arm Marazzo *et al*(19) RCT. Meta-analyses could thus not be conducted owing to this paucity of studies, thus we cannot provide pooled estimates for effectiveness of any of the study products. In a random sample by Marrazzo *et al*, TFV was detected in 29% of available plasma samples from participants randomly assigned to receive TDF-FTC(19). In the study by van Damme *et al*, less than 40% of the HIV-uninfected women in the TDF-FTC group had evidence of recent pill use at visits that were matched to the HIV-infection window for women with seroconversion(18).

Discussion

This systematic review involving the synthesis of evidence from four studies(16–18,21) that evaluated the effectiveness of TFV-based PrEP is one of the few reviews that has been conducted with emphasis on the use of PrEP prophylaxis to reduce transmission among SSA African women. Given that this population has unique socio-cultural and economic dynamics that place them at a higher risk of HIV acquisition(6,22–24), studies exploring effective prevention methods form the crux of reducing their HIV burden(25). Though our synthesis suggests that TFV might not be effective in pre-exposure prophylaxis of HIV in this unique population, we critically appraised the evidence and unveiled poor adherence as a caveat that may guide researchers intending to conduct future studies in this or related domains.

Effectiveness was defined as the ability to prevent HIV infections in women on study products versus placebos and reported as IRRs or HRs. The IRR gave the relative differences in the HIV incidence rates in the active versus placebo arms whilst the HRs obtained from Cox regression models denoted the hazard of acquiring the infection for participants on active products over those on the placebo. We examined the effectiveness of TFV-1% vaginal gel, oral TDF and TDF-FTC against placebo but not against each other. Comparing them against each other and against placebo is called a network meta-analysis(26), and it useful for health technology assessment and economic evaluations; however, this requires significant expertise.

None of the study products conferred statistically significant protection against HIV acquisition. The design, conduct and trial characteristics were similar though the dosing strategy for the gel was different(17–19). The RCTs reviewed were well conducted, with low to medium risk of bias. They enrolled the appropriate group of SSA women at risk, aged 18-45 years. However, they were affected by premature stoppages resulting in inadequate follow-up or sample size, thus losing statistical power(16,18,19). Low statistical power reduces chances of detecting the true effect but also reduces chances that a statistically significant effect represents a true effect. Thus, attaining adequate power is critical for high quality RCTs.

Jiang *et al* conducted a meta-analysis of all TFV-PrEP (gel, TDF and TDF-FTC) against placebo and obtained 47% effectiveness (RR 0.53, 95% CI 0.40-0.71)(27). This improved to 51% effectiveness (RR 0.49, 95% CI 0.38-0.63) in sensitivity analysis after excluding two studies with non-significant results. Seven RCTs were reviewed but Marrazzo *et al*(19) was not included. Heterogeneous populations were included (TGW MSM, Intravenous Drug Users (IDUs) and heterosexual men and women). Owing to differential risk perceptions, sexual behaviours, socioeconomic characteristics it may not be appropriate to pool evidence from diverse key populations. Moreover, this meta-analysis was inappropriate because they conducted a pairwise meta-analysis where they combined the three interventions against a placebo. These three are unlikely to be equally efficacious and therefore should not be pooled together. Instead, a network meta-analysis may have been more appropriate(26).

Similarly, Okwundu *et al* found PrEP to be effective at reducing risk of HIV infection in a Cochrane systematic review, with a statistically significant 51% reduction (RR 0.49, 95% CI 0.28-0.85) for TDF-FTC versus placebo and a statistically significant 67% reduction (RR 0.33, 95% CI 0.22-0.55) for TDF versus placebo(28). The review included MSM, TGW, IDUs and heterosexual men and women across the world. The trial by Marrazzo *et al*(19) was not yet reported. When considering the effectiveness across SSA women these results may not be generalisable, thus the need for this review which was specific. Some of the studies we reviewed were stopped prematurely due to lack of efficacy(18,19). While TFV-PrEP was protective of HIV acquisition in other populations, poor adherence was the caveat in the RCTs evaluating the effectiveness in women residing in SSA.

Objective measures of adherence in TFV-PrEP studies conducted in at-risk women residing in SSA consistently revealed low adherence, discordant from subjective reports(29–33). Low adherence was noted in MTN-020, a study that evaluated the effectiveness (27%, 95% CI 1-46%) of a dapivirine vaginal ring against placebo in the same population(34). When stratified according to adherence levels, the protective effect (37%, 95% CI 12-56%) of dapivirine increased by 10% in high-adherers(34). That higher adherence is associated with a higher protective effect is also supported by evidence from Karim *et al* and Marrazzo *et al*(17,19). A drug works best if it is in the right place, at the right time and in the right concentration. Qualitative studies among MSM reflect higher risk perception and commitment to PrEP, translating into higher adherence and effectiveness(35). Detected blood levels of TDF-FTC strongly correlated with protective effect in the iPrEx trial(36,37). As research advances towards multi-purpose prevention technologies for HIV, STIs and pregnancy, understanding the reasons why adherence remains

low in this key at-risk population is critical, as the progress and success of future clinical trials premises upon addressing the inadequacies of adherence.

Strengths

This systematic review was conducted and reported using the PRISMA-2009 guidelines(10), following a protocol that had been developed according to PRISMA-P 2015 guidelines(11). This is now considered the gold standard for conducting and reporting systematic reviews. Multiple databases were searched to maximise chances of retrieving all eligible studies and minimise bias as per Cochrane recommendations(12); registries of trials were searched to note completed and ongoing trials. The literature search was progressively built from an initial scoping search in MEDLINE, from which the comprehensive final search was refined. Sensitivity-maximising filters from the Cochrane Collaboration and SIGN were utilised to identify all eligible studies. There was no language restriction to eliminate language bias, though all the eligible studies were in English, negating the need for translation. By sticking to PRISMA and Cochrane guidelines, this review was meant to be replicable.

The studies included in this review were all carried out among SSA women, absolute age ranges 18-45 years, the group at highest risk of HIV acquisition, with comparable demographic and socio-economic characteristics. The multi-centre, multi-national RCTs extend external validity to comparable populations across SSA.

Limitations

A limited number of studies were retrieved. Thus, publication bias and statistical heterogeneity could not be explored. Meta-analyses, funnel plots, meta-regression and cumulative meta-analysis, which allow further explorations, as well as sensitivity analyses, could not be conducted. We could not provide pooled effect size estimates of interventions owing to paucity of studies.

Implications for Public Health and Research

The burden of HIV among young SSA women remains substantial. Preventive public health interventions are the key to curtailing further infections, and whilst the search for an effective vaccine continues, we must investigate other effective interventions in addition to the array that already exists. TVF-PrEP offers such an attractive choice for women. Whilst in September 2015 the WHO recommended the daily use of TFV-PrEP in at-risk groups such as MSM, TGW and heterosexual men and women in sero-discordant couples(4), the evidence to extend this intervention to SSA women remains missing. Whilst exploring further the reasons for effectiveness, the search for other effective interventions to protect SSA women from HIV acquisition must continue. As science advances towards multipurpose prevention technologies

for women, barriers towards uptake of protective interventions that work in other populations must be addressed among SSA women.

Conclusion

None of the study products, TFV-1% vaginal gel, oral TDF and TDF-FTC conferred statistically significant protection against HIV acquisition in young at-risk SSA women. The current evidence does not support the effectiveness of TFV in the pre-exposure prophylaxis for HIV among women residing in SSA. Due to the paucity of studies, more studies are needed and factors that may affect effectiveness such as adherence need to be further explored.

Abbreviations

SSA: Sub-Saharan Africa. TFV: tenofovir, PrEP: Pre-Exposure Prophylaxis. HIV: Human Immunodeficiency Syndrome. TDF: tenofovir disoproxil fumarate. FTC: emtricitabine. TDF-FTC: Truvada. RCT: Randomised Controlled Trial. HR: hazard ratio. OR: odds ratio. RR: relative risk. IRR: incidence rate ratio. PROSPERO: International Prospective Register of Systematic Reviews. UNAIDS: United Nations Programme on HIV/AIDS. MSM: men who-have-sex-with men. TGW: transgender women. CI: confidence interval. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis. PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol. MeSH: Medical Subject Headings. SIGN: Scottish Intercollegiate Network. CONRAD: Contraception Research and Development. USAID: United States Agency for International Development. FHI-360: Family Health International 360. CAPRISA: Centre for the AIDS Programme of Research in South Africa. NIH: National Institutes for Health. IDU: Intravenous Drug User. MTN: Microbicide Trials Network. iPrEx: Pre-exposure Prophylaxis Initiative/Iniciativa Profilaxis Pre Exposicioni. FACTS: Follow-on African Consortium for Tenofovir Studies.

Ethics Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The authors consent to make available all data and material through gmurewanhema@yahoo.com.

Funding

There was no funding for this project.

Competing interests

None to declare for all authors.

Acknowledgements

We are grateful to the UK Foreign and Commonwealth Office who sponsored us to undertake our postgraduate studies through Chevening Scholarships at the University of Glasgow where this concept was originally developed.

Author Contributions

GM identified the concept and developed the primary manuscript. He performed the literature search, screened articles for eligibility and drafted the primary manuscript. MM and NT performed literature searches independently. All authors made contributions to the final manuscript.

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Figure Legends

Figure 1: PRISMA Flow Diagram

Figure 2: Risk of Bias across Included Studies.

Table Legends

Table 1: Characteristics of Included Studies

Table 2: Summary data for effectiveness of TFV-1% vaginal gel, oral TDF and TDF-FTC against their respective placebos

Appendices Legends

Appendix 1: OVID MEDLINE search strategy

Appendix 2: OVID Embase Search Strategy

Appendix 1: OVID MEDLINE Search Strategy

Database: Ovid MEDLINE(R) <1946 to July Week 4 2020>

Search Strategy:

- 1 HIV*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (280737)
- 2 human immunodeficiency virus.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (79509)
- 3 retrovir*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (54964)
- 4 wom*n.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (838079)
- 5 female*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (7322079)
- 6 tdf*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1758)
- 7 tenofovir*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4002)
- 8 truvada.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (92)
- 9 emtricitabine-tenofovir.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (370)
- 10 ftc-tdf.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (103)
- 11 prophylaxis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (81609)
- 12 prevent*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1036663)
- 13 protect*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (587561)
- 14 reduc*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2402007)
- 15 1 or 2 or 3 (326751)
- 16 4 or 5 (7358230)
- 17 6 or 7 or 8 or 9 or 10 (4955)
- 18 11 or 12 or 13 or 14 (3595902)
- 19 15 and 16 and 17 and 18 (701)
- 20 randomi*ed controlled trial.pt. (414789)
- 21 controlled clinical trial.pt. (90619)

22 randomi*ed.ab. (373008)
23 placebo.ab. (158104)
24 drug therapy.fs. (1852228)
25 randomly.ab. (220170)
26 trial.ab. (322366)
27 groups.ab. (1389663)
28 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (3527027)
29 exp animals/ not humans.sh. (4236009)
30 28 not 29 (3005492)
31 19 and 30 (497)
32 limit 31 to yr="2000 -Current" (495)

Appendix 2: OVID Embase Search Strategy

Database: Embase 1947-Present, updated daily

Search Strategy:

-
- 1 HIV*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (319588)
 - 2 human immun*deficiency virus.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (360213)
 - 3 retrovir*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (62666)
 - 4 wom*n.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1256064)
 - 5 female*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (7189408)
 - 6 tdf*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3911)
 - 7 tenofovir*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (18062)
 - 8 truvada.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1197)
 - 9 emtricitabine-tenofovir.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (489)
 - 10 ftc-tdf.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (368)
 - 11 prophylaxis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (187124)
 - 12 prevent*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1687282)
 - 13 protect*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (899055)
 - 14 reduc*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3655945)
 - 15 1 or 2 or 3 (447996)
 - 16 4 or 5 (7355390)
 - 17 6 or 7 or 8 or 9 or 10 (19660)
 - 18 11 or 12 or 13 or 14 (5544387)
 - 19 15 and 16 and 17 and 18 (2133)
 - 20 Clinical trial/ (866264)
 - 21 randomised controlled trial/ (403095)
 - 22 randomisation/ (70523)
 - 23 single blind procedure/ (22076)
 - 24 double blind procedure/ (132821)
 - 25 crossover procedure/ (47294)
 - 26 placebo/ (291211)
 - 27 randomi?ed controlled trial\$.tw. (134965)
 - 28 rct.tw. (20256)
 - 29 random allocation.tw. (1595)
 - 30 randomly allocated.tw. (24879)
 - 31 allocated randomly.tw. (2138)
 - 32 (allocated adj2 random).tw. (909)
 - 33 single blind\$.tw. (17637)
 - 34 double blind\$.tw. (171349)
 - 35 ((treble or triple) adj blind\$.tw. (590)

36 placebo\$.tw. (241545)
37 prospective study/ (333541)
38 or/20-37 (1598820)
39 case study/ (46899)
40 case report.tw. (330537)
41 abstract report/ or letter/ (977100)
42 or/39-41 (1347515)
43 38 not 42 (1557286)
44 19 and 43 (693)
45 limit 44 to yr="2000 -Current" (692)

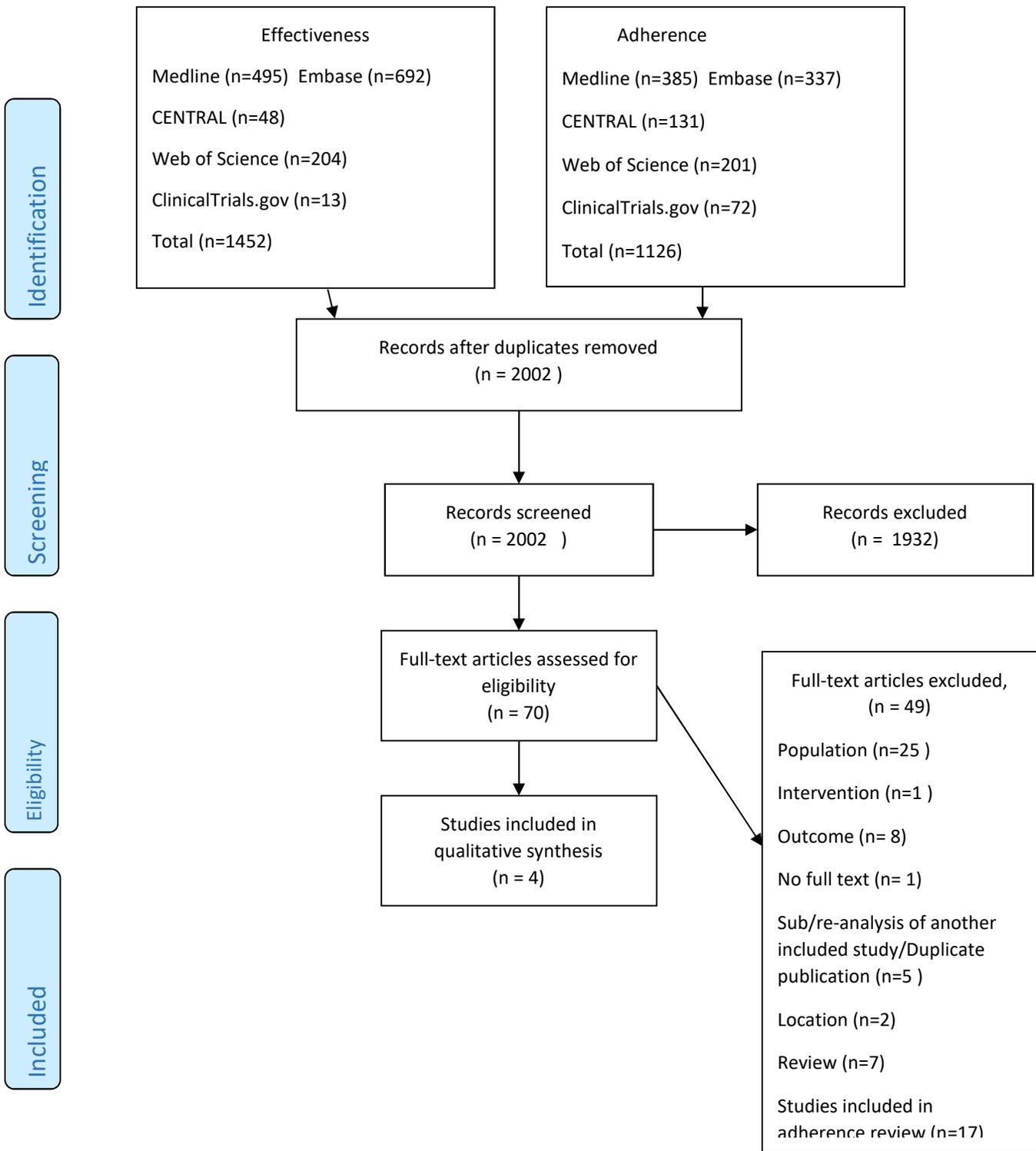


Figure 1: PRISMA Flow Diagram: the search was conducted for effectiveness and adherence

Author, Year of Publication, Journal, Trial name	Location	Funding Source/ Author Declaration of financial interest	Study Design / Study Products	Number of Participants / follow-up	Study participants characteristics
Karim QA et al, 2010, <i>Science</i> CAPRISA-004(38) (And Mansoor et al, 2014, <i>AIDS Behav</i>)(33)	2 CAPRISA Clinical Research Sites, KwaZulu-Natal, South Africa	<u>Sponsors</u> : USAID, FHI-360. <u>Study products</u> : CONRAD, Gilead Sciences. <u>Competing interests</u> : Lead author was co-principal investigator for HPTN. No other competing interests declared.	<u>Design</u> : Phase 2b double-blind, placebo-controlled RCT. <u>Products</u> : TFV-1% vaginal gel and placebo gel.	889 participants (445 TFV arm, 444 placebo arm). Enrolment and follow-up for 21 months from May 2007 to January 2009.	<u>Rural women</u> : n=611. Mean age 23.3 years, range 18-40 years. 6.5% married. 77% stable partner. Mean number of lifetime sexual partners 2.1. <u>Urban women</u> : n=278. Mean age 25.1 years, range 18-40 years, 3.6% married, 93.1% stable partner. Mean number of lifetime sexual partners 6.0.
Peterson L et al, 2007, <i>PLoS Clinical Trials</i> (16)	Research Sites in Tema, Ghana; Douala, Cameroon and Ibadan, Nigeria	<u>Sponsors</u> : Bill and Melinda Gates Foundation and FHI-360. <u>Study product</u> : Gilead Sciences. <u>Competing interests</u> : One author was with the Bill and Melinda Gates Foundation and another with Gilead Sciences. Both contributed to study design and manuscript writing and publication decision. Another author was both an employee and shareholder of Gilead Sciences.	<u>Design</u> : Phase 2 double-blind, placebo-controlled RCT. <u>Products</u> : TDF 300mg and oral placebo	936 participants. 469 on TDF (Ghana 200, Cameroon 200 and Nigeria 69). 467 on placebo (Ghana 200, Cameroon 200, Nigeria 67). Enrolled and followed up monthly between June 2004 and March 2006.	Mean age: TDF group 23.6±3.9 years; placebo group 23.5±3.9 years. Not married: TDF group 92.7%, placebo group 89.1%
Marrazzo JM et al, 2015, <i>N Eng J Med</i> VOICE/MTN-003(19)	15 Clinical Research Sites in South Africa, Uganda and Zimbabwe	<u>Sponsors</u> : NIH <u>Study products</u> : CONRAD and Gilead Sciences. <u>Competing interests</u> : No conflicting financial interests were disclosed.	<u>Design</u> : Phase 2b double-blind, placebo-controlled RCT <u>Products</u> : TFV-1% vaginal gel, placebo gel, TDF 300mg and TDF-FTC 300mg/200mg and oral placebo.	5029 participants. TDF 1007, TDF-FTC 1003, Oral placebo 1009, TFV gel 1007, placebo gel 1003. Enrolled and followed-up monthly from September 2009 to June 2011	Mean age 25.3±5.2 years, 21% married, 22% had ≥2 male partners in the past 3 months.
Van Damme L, et al, 2012, <i>N Eng J Med</i>	Clinical Research Sites in	<u>Sponsor</u> : USAID and Bill and Melinda Gates Foundation. <u>Study product</u> : Gilead Sciences	<u>Design</u> : Phase 3 double-blind	2120 participants. (63 Arusha, 739 Bondo, 554 Bloemfontein, 764	Mean age 24.2 years (median 23 years, range 18-35). 30.9% married. 12.6% reported sex for

FEM-PrEP(18)	Arusha, Tanzania; Bondo, Kenya and Bloemfontein and Pretoria, South Africa.	<u>Competing interests:</u> No significant financial interests were declared.	placebo-controlled RCT. <u>Product:</u> TDF-FTC 300mg/200mg and oral placebo	Pretoria). TDF-FTC 1062, Placebo 1058. Enrolled and followed-up monthly from June 2009 to April 2011.	money or gifts with a non-primary partner in the previous 4 weeks.
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Figure 2: Risk of Bias Assessments

Domain				
	Karim et al 2010 (& Mansoor et al 2014)	Peterson et al 2007	Marrazzo et al 2015	Van Damme et al 2012
Adequate sequence generation				
Allocation concealment				
Blinding				
Incomplete outcome data addressed				
Free of selective reporting				
Free of other bias				
Total	5	4	5	3

Key: Ticked icon: low-risk, Cross: high-risk, exclamation mark: unclear risk

mark: unclear risk

Table 2: Summary Data for Effectiveness of TFV-1% vaginal gel, oral TDF and TDF-FTC against Placebos

Product	Study	HIV endpoints/ No of Participants	HIV Incidence/100 women-years (95% CI)	HIV Incidence Rate ratio (±95% CI)	Adjusted Hazard ratio (95% CI)	Effectiveness (95% CI)	Risk of Bias
TFV gel	Karim et al, <i>Science</i> 2010(38)	TFV gel arm: 38/ 445. Placebo arm: 60/ 444	TFV gel arm, 5.6 (4.0-7.7) Placebo arm, 9.1 (6.9-11.7)	0.61	0.63, (0.42- 0.94) p=0.025	37% (6-58), statistically significant	Low
	Marrazzo et al, <i>NEJM</i> , 2015(19)	TFV gel arm: 61/ 1007 Placebo arm: 70/ 1003	TFV gel arm, 6.0 (4.6-7.6) Placebo arm, 6.8 (5.3-8.6)	0.88	0.85 (0.61- 1.21) p=0.37	15% (-21 to 39%), not statistically significant	Low
Oral TDF	Peterson et al, <i>PLoS Clinical Trials</i> , 2007(16)	TDF arm: 2, 469 Placebo arm: 6, 467	TDF arm, 0.86 Placebo arm, 2.48	0.35 (0.03- 1.93) p=0.24	-	65% (-93, 97%), statistically not significant	Medium
	Marrazzo et al, <i>NEJM</i> , 2015(19)	TDF arm: 52, 1007 Placebo arm: 35, 1009	TDF arm, 6.3 (4.7- 8.3) Placebo arm, 4.2 (2.9-5.8)	1.50	1.49 (0.97- 2.29) p=0.07	49% increased risk, not statistically significant	Low
TDF- FTC	Van Damme et al, <i>NEJM</i> , 2012(18)	TDF-FTC arm: 33, 1024 Placebo arm: 35, 1032	TDF-FTC arm: 4.7 Placebo arm: 5.0	0.94	0.95 (0.59- 1.54) p=0.84	5% (-54 to 41%), not statistically significant	Medium
	Marrazzo et al, <i>NEJM</i> , 2015(19)	TDF-FTC arm: 61, 1003 Placebo arm: 60, 1009	TDF-FTC arm, 4.7 (3.6-6.1) Placebo arm, 4.6 (3.5-5.9)	1.02	1.04 (0.73- 1.49) p=0.81	4% increased risk (-49 to 27%), not statistically significant	Low