Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

Okwundu CI, Uthman OA, Okoromah CAN

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Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

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ABSTRACT

Background

More than 30 years into the global HIV/AIDS epidemic, infection rates remain alarmingly high, with over 2.7 million people becoming infected every year. There is a need for HIV prevention strategies that are more effective. Oral antiretroviral pre-exposure prophylaxis (PrEP) in high-risk individuals may be a reliable tool in preventing the transmission of HIV.

Objectives

To evaluate the effects of oral antiretroviral chemoprophylaxis in preventing HIV infection in HIV-uninfected high-risk individuals.

Search methods

We revised the search strategy from the previous version of the review and conducted an updated search of MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE in April 2012. We also searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov for ongoing trials.

Selection criteria

Randomised controlled trials that evaluated the effects of any antiretroviral agent or combination of antiretroviral agents in preventing HIV infection in high-risk individuals

Data collection and analysis

Data concerning outcomes, details of the interventions, and other study characteristics were extracted by two independent authors using a standardized data extraction form. Relative risk with a 95% confidence interval (CI) was used as the measure of effect.

Main results

We identified 12 randomised controlled trials that meet the criteria for the review. Six were ongoing trials, four had been completed and two had been terminated early. Six studies with a total of 9849 participants provided data for this review. The trials evaluated the following: daily oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) versus placebo; TDF versus placebo and daily TDF-FTC versus intermittent TDF-FTC. One of the trials had three study arms: TDF, TDF-FTC and placebo arm. The studies were...
carried out amongst different risk groups, including HIV-uninfected men who have sex with men, serodiscordant couples and other high risk men and women.

Overall results from the four trials that compared TDF-FTC versus placebo showed a reduction in the risk of acquiring HIV infection (RR 0.49; 95% CI 0.28 to 0.85; 8918 participants). Similarly, the overall results of the studies that compared TDF only versus placebo showed a significant reduction in the risk of acquiring HIV infection (RR 0.33; 95% CI 0.20 to 0.55, 4027 participants). There were no significant differences in the risk of adverse events across all the studies that reported on adverse events. Also, adherence and sexual behaviours were similar in both the intervention and control groups.

**Authors’ conclusions**

Finding from this review suggests that pre-exposure prophylaxis with TDF alone or TDF-FTC reduces the risk of acquiring HIV in high-risk individuals including people in serodiscordant relationships, men who have sex with men and other high risk men and women.

**PLAIN LANGUAGE SUMMARY**

**Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals**

This review evaluated the effects of giving people at high risk for HIV infection drugs to prevent infection (called antiretroviral pre-exposure prophylaxis, or PrEP). We found six randomised controlled trials that assessed the effects of oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) versus placebo; TDF versus placebo, and daily TDF-FTC versus intermittent TDF-FTC. One of the trials had three study arms (TDF, TDF-FTC and placebo arm). The trials were carried out amongst different risk groups, including HIV-uninfected men who have sex with men, people in serodiscordant sexual relationships where one partner is infected and the other is not, and other high risk men and women. The findings suggest that the use of TDF alone or TDF+FTC reduces the risk of becoming infected with HIV. However, further studies are need to evaluate the method of administration (daily versus intermittent dosing), long-term safety and cost effectiveness of PrEP in different risk groups and settings.
**SUMMARY OF FINDINGS FOR THE MAIN COMPARISON**

Tenofovir + Emtricitabine compared to placebo for preventing HIV in high-risk individuals

**Patient or population:** High-risk HIV-uninfected individuals (including serodiscordant couples, men who have sex with men and sex workers)

**Settings:** High, middle and low income settings

**Intervention:** Oral Tenofovir + Emtricitabine

**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<td>Placebo</td>
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<tr>
<td>TDF + FTC</td>
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<tr>
<td>HIV infection</td>
<td>Study population</td>
<td>RR 0.49 (0.28 to 0.85)</td>
<td>8813 (4 studies)</td>
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<td>19 per 1000 (11 to 33)</td>
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<td>Serious adverse events</td>
<td>Study population</td>
<td>RR 1 (0.83 to 1.19)</td>
<td>6862 (3)</td>
<td>⊕⊕⊕ Moderate¹</td>
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<td>65 per 1000</td>
<td>65 per 1000 (54 to 77)</td>
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*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

¹ We downgraded the quality of evidence by one level on account of instability of results since there are fewer than 200 events per arm.
BACKGROUND

The global incidence of HIV infection has been declining in many countries, with a total of 2.7 million infections in 2010 compared to 3.1 million in 2001 (WHO 2011). However, incidence still remains high, and Sub-Saharan Africa continues to bear much of the global HIV burden. In 2010, about 68% of all people living with HIV in the world resided in the sub-Saharan Africa (WHO 2011). To stem the high infection rate, safe and effective approaches to HIV prevention are needed. Behaviour change programmes have contributed to reductions in the number of new infections in many countries, but too many people remain at high risk.

Biomedical tools in combination with effective behavioral interventions are required to adequately curb the spread of the virus (Derdelinckx 2006). Antiretroviral drugs are also currently used to prevent HIV transmission in various settings. In a double blind microbicide trial conducted in South Africa, a vaginal gel containing tenofovir disoproxil fumarate (TDF) plus emtricitabine ( FTC) preparation was found to be 39% per cent effective in reducing HIV transmission among women considered to be at high risk of HIV infection (Abdool Karim 2010). There is substantial evidence that timely administration of antiretroviral drugs reduces the risk of HIV transmission from HIV-infected mothers to their infants in the prenatal and perinatal periods (Guay 1999; Siegfried 2001). Antiretroviral drugs are currently the cornerstone of prevention of mother-to-child transmission of HIV. Early initiation of antiretroviral therapy (ART) has been shown to reduce the rate of sexual transmission of HIV-1 and clinical events in couples in serodiscordant couples (Anglemyer 2011; Cohen 2011; Donnell 2010). Also, post-exposure prophylaxis (PEP) has been shown to reduce the risk of HIV infection after occupational percutaneous or mucous membrane exposure to HIV because of a needlestick injury or after unprotected sexual intercourse if administered shortly after exposure (Smith 2005; Young 2007).

Description of the intervention

Pre-exposure prophylaxis (PrEP) is a new approach in which antiretroviral drugs are taken by an HIV-uninfected individual prior to HIV exposure to reduce the likelihood of infection. It should be distinguished from PEP, in which an uninfected individual takes antiretroviral drugs soon after a potential HIV exposure, with the aim of reducing the likelihood of infection (Sharif-Azad 2011). Two promising drugs that are currently being considered for use in HIV pre-exposure prophylaxis are TDF and the combination TDF-FTC. TDF and FTC are both nucleoside analogue reverse transcriptase inhibitors. These medications have been chosen as agents for PrEP because of their excellent safety record, a favourable resistance profile and limited side effects (Derdelinckx 2006). These drugs stop HIV from multiplying by preventing the reverse transcriptase enzyme from transcribing HIV genetic material (RNA) into DNA before the virus's genetic code is inserted into an infected cell's genome.

How the intervention might work

Chemoprophylaxis currently is used to protect people from many other infections such as malaria and influenza. Also, current chemoprophylaxis for HIV-infected patients with advanced immunodeficiency is recommended for the prevention of Pneumocystis jiroveci pneumonia, Toxoplasma encephalitis and Mycobacterium avium complex infections. Research has demonstrated the ability of antiretrovirals to reduce the risk of transmission in monkeys of simian immunodeficiency virus (SIV), a virus commonly used in primate research to model HIV infection in humans (García-Lerma 2008; Subbarao 2006). Antiretrovirals have also been shown to be effective preventing HIV infection when used in mice that are susceptible to intravaginal infection with HIV (Denton 2008). Theoretically, if replication can be stopped when HIV first enters the body, the virus will not be able to establish a permanent infection (Haase 2010). It is reasonable to assume that PrEP might offer some degree of protection. HIV pre-exposure prophylaxis could be a viable prevention strategy for certain people at high risk of HIV infection, such as commercial sex workers, people in serodiscordant relationships and members of high-risk groups who choose not to use condoms or for whom consistent condom use has proven difficult (Youle 2003).

Why it is important to do this review

Research into PrEP has stirred international controversy due to various issues of concern (AIDS 2005). One concern is the long-term side effects of antiretroviral drugs used over many years by uninfected individuals. With TDF, the potential risks include kidney toxicity, loss of bone density, and liver inflammation “flares” in people with hepatitis B (Highleyman 2006). Other concerns regarding PrEP are drug adherence and resistance. Any resistance developed to antiretroviral drugs such as TDF when used first for HIV prevention could limit the usefulness of the drugs later for HIV treatment (Bahuguna 2006). There also are concerns that PrEP will lead to an increase in high-risk behaviour (AFAO 2005). If PrEP is not completely effective, even a partial reduction in use of safer sex could lead to an increased rate of HIV transmission (Highleyman 2006). Intensive risk reduction counselling could prevent such behavioural disinhibition. This review aims to summarise all the available evidence on the efficacy and safety of oral antiretroviral PrEP for HIV prevention.

OBJECTIVES

To evaluate the effects of oral antiretroviral chemoprophylaxis in preventing HIV infection in HIV-uninfected high-risk individuals.
METHODS

Criteria for considering studies for this review

Types of studies
We included randomised controlled trials that evaluated the effects of antiretroviral chemoprophylaxis in preventing HIV infection in high-risk individuals.

Types of participants
HIV-uninfected:
- Commercial sex workers
- Individuals in serodiscordant relationships
- Injection drug users
- Men who have sex with men (MSM)
- Sexually active young adults

We did not include studies involving pregnant women and the prevention of mother-to-child transmission.

Types of interventions
We investigated trials comparing various types of oral PrEP regimens:
- TDF only versus placebo or no treatment
- TDF + FTC versus placebo or no treatment
- TDF only versus TDF + FTC
- Any other oral PrEP regimen

We did not include studies involving topical application of antiretrovirals (e.g., vaginal gels).

Types of outcome measures

Primary
HIV incidence

Secondary
Adherence to PrEP (as measured by the primary studies).

Adverse effects
Frequency and type of adverse effects or complications.

Search methods for identification of studies

Electronic searches
See: HIV/AIDS Cochrane Review Group search strategy. Identification of studies was done with the assistance of the HIV/AIDS Review Group Trials Search coordinator. We revised the search strategy from the previous version of the review and conducted a comprehensive search to identify all relevant studies regardless of language or publication status (i.e. published, unpublished, in press, and in progress).

We conducted an updated search of the following electronic databases on 20 April 2012:
- MEDLINE via PubMed, 1980 to 20 April 2012
- The Cochrane Central Register of Controlled Trials
- EMBASE, 1980 to 20 April 2012

The detailed search strategies for each of the databases are documented in Table 1, Table 2, and Table 3, respectively.

We also searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov for ongoing or prospective trials.

Searching other resources

Hand searches of the reference lists of all included studies was performed. We searched for any the on-going or prospective studies in the WHO Clinical Trials Registry platform and ClinicalTrials.gov. We also searched AEGIS for conference abstracts.

Data collection and analysis

Selection of studies
Two authors (CO and OU) independently read the titles, abstracts, and descriptor terms of the search output from the different databases to identify potentially eligible studies. Full text articles were obtained for all citations identified as potentially eligible.

Both authors (CO and OU) independently inspected these to establish the relevance of the articles according to the pre-specified criteria. Studies were reviewed for relevance based on study design, types of participants, interventions, and outcome measures. We gave reasons for excluding potentially relevant studies in an excluded studies table.

Data extraction and management

We extracted data independently using the form we designed and agreed upon. Both authors verified the extracted data. Extracted information included the following.
- Study details: citation, study design and setting, time period and source of funding.
• Participant details: study population demographics, risk characteristics, population size and attrition rate.
• Intervention details: type of drug, comparator, dose, duration and route of administration.
• Outcome details: incidence of HIV infection (including type of laboratory tests used to confirm HIV diagnosis before and after administering PrEP), degree of adherence to PrEP and adverse effects.

We summarised the eligible study using the RevMan software. The authors independently extracted the data and entered them into RevMan; all entries were rechecked by both authors, and all disagreements were resolved by discussion.

Assessment of risk of bias in included studies
CO and OU independently examined the components of each included trial for risk of bias using a standard form. This included information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the studies were assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions. Where differences arose, they were resolved by discussions with the third reviewer.

Sequence generation
• Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelope shuffling, etc.
• Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number.
• Unclear: insufficient information to permit judgement of the sequence generation process.

Allocation concealment
• Adequate: participants and the investigators enrolling participants cannot foresee assignment (e.g., central allocation; or sequentially numbered, opaque, sealed envelopes).
• Inadequate: participants and investigators enrolling participants can foresee upcoming assignment (e.g., an open random allocation schedule (e.g., a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered).
• Unclear: insufficient information to permit judgement of the allocation concealment or the method not described.

Blinding
• Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias.
• Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding.
• Unclear: insufficient information to permit judgement of adequacy or otherwise of the blinding.

Incomplete outcome data
• Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups.
• Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data.
• Unclear: insufficient reporting of attrition or exclusions.

Selective Reporting
• Adequate: a protocol is available which clearly states the primary outcome as the same as in the final trial report.
• Inadequate: the primary outcome differs between the protocol and final trial report.
• Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.

Other forms of bias
• Adequate: there is no evidence of bias from other sources.
• Inadequate: there is potential bias present from other sources (e.g., early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).
• Unclear: insufficient information to permit judgement of adequacy or otherwise of other forms of bias.

Measures of treatment effect
Outcome measures for dichotomous data (e.g., HIV infection) were calculated as a relative risk (RR) with 95% confidence intervals (CI).

Dealing with missing data
We contacted the study authors to provide further information on the results of some of the studies.

Assessment of heterogeneity
In the meta-analysis, we assessed statistical heterogeneity using the chi square and I squared statistics.
Data synthesis

CO and OU independently extracted data from the included studies. The data was summarised in RevMan 5.1. All of the entries were rechecked by both authors. Where possible, we pooled the results from the included studies in a random effects meta-analysis, using the Mantel-Haenzel odds ratio. We performed a subgroup analysis by stratifying our analysis by the type of antiretroviral (TDF versus placebo and TDF-FTC versus placebo) and also by risk group (heterosexual versus men who have sex with men).

Results of the search

We identified 12 relevant studies from a total of 2684 titles and abstracts from the search Figure 1. Of the 12 studies, six were ongoing, and six studies provided data for this review (Baeten 2012; Van Damme 2012; Grant 2010; Mutua 2010; Peterson 2007; Thigpen 2012). Two of the studies (Peterson 2007; Van Damme 2012) that provided data for this review were terminated early. We contacted the study authors where necessary for additional information.

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies. See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies; Characteristics of studies awaiting classification.
Figure 1. Study flow diagram.

1 study included in the previous version of the review

2684 records identified through the updated search

2684 records screened

2672 records excluded

12 relevant studies identified (6 ongoing studies)

6 studies identified

6 studies included in the analysis

(The six studies identified in the updated search includes the study in the previous version of the review)
**Types of participants and settings**

The studies involved HIV-uninfected participants from different risk groups: 2499 men who have sex with men aged 18 years and above (Grant 2010), 936 high risk women age 18 to 35 years (Peterson 2007), 144 high-risk men and women (67 men who have sex with men, 5 female sex workers and 72 serodiscordant couples: 36 men and 36 women) aged 18 to 49 years (Mutua 2010), 4758 serodiscordant couples (men and women aged 18 to 65 years) (Baeten 2012), 1200 heterosexual men and women aged 18–39 (Thigpen 2012) and 2120 high-risk women aged of 18 to 35 years (Van Damme 2012). The participants in Peterson 2007 trial lived in areas within each city that were considered to be at high risk for HIV transmission and were also at high risk of acquiring HIV infection by virtue of having three or more coital acts per week and four or more sexual partners per month. Mutua 2010 was conducted in Kenya, and Thigpen 2012 was conducted in Botswana. Four of the studies (Baeten 2012; Grant 2010; Van Damme 2012 and Peterson 2007) were multinational trials. Baeten 2012 study was conducted in Kenya and Uganda; Grant 2010 study was conducted in Peru, Ecuador, South Africa, Brazil, Thailand and the United States of America; Peterson 2007 study was conducted in Cameroon, Ghana and Nigeria; and Van Damme 2012 study was conducted in Kenya, South Africa, Tanzania and Zimbabwe.

**Types of intervention**

The interventions tested in the studies were daily oral TDF vs placebo (Peterson 2007), daily oral TDF-FTC vs placebo (Grant 2010; Van Damme 2012), daily oral TDF-FTC vs. intermittent oral TDF-FTC (Mutua 2010), and daily oral TDF-FTC vs placebo (Thigpen 2012). One of the studies had three arms: TDF, TDF-FTC and placebo (Baeten 2012).

**Types of outcome measures**

The outcomes reported in the studies were HIV incidence, safety end points, adverse events, sexual behaviour and adherence.

**Risk of bias included studies**

See Risk of Bias graph and Risk of Bias summary tables for the included studies Figure 2; Figure 3. In general, the overall methodological quality of the studies was acceptable. We obtained additional information from conference presentations and by contacting the study authors to be able to make assessments where necessary.

---

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

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding (performance bias and detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
Figure 3. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

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<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding (performance bias and detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
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<td>Baeten 2012</td>
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Allocation
The method of sequence generation was adequate in all the studies. Allocation concealment was also adequate in all the studies except in the Grant 2010 study where we did not find information on allocation concealment.

Blinding
Allocation to the intervention or placebo was blinded to study participants and investigators in all the included studies. However, in Mutua 2010, allocation to daily or intermittent dosing was not blinded.

Incomplete outcome data
There were similar rates of attrition in both the placebo and treatment arms in the studies (Baeten 2012; Van Damme 2012; Grant 2010; Thigpen 2012). In Mutua 2010 there was no loss to follow-up in any of the study arms. In Peterson 2007 because of irregularities in the performance of the laboratory in Nigeria, data from that site were excluded from the primary safety analyses.

Selective reporting
We compared the reports with the entries into the clinical trial registries and did not find any evidence of selective outcome reporting in any of the studies.

Other potential sources of bias
One of the trial sites for the Peterson 2007 study was closed early because of repeated noncompliance with the trial protocol. We did not explore the potential for publication bias because of the small number of included studies.

Effects of interventions
See: Summary of findings for the main comparison TDF+ FTC compared to placebo for preventing HIV in high-risk individuals; Summary of findings 2 TDF compared to placebo for preventing HIV in high-risk individuals

HIV Incidence
Four studies that compared TDF-FTC with placebo reported HIV incidence (Baeten 2012; Van Damme 2012; Grant 2010; Thigpen 2012). The meta-analysis revealed significantly lower HIV incidence in participants who received TDF-FTC compared to those who received placebo (Mantel-Haenzel random effects RR (RRMHRE) 0.49; 95% CI 0.28 to 0.85; 8918 participants). There was substantial statistical heterogeneity ($I^2 = 77\%$, $p=0.005$) (Figure 4; Analysis 1.1). Two RCTs that compared TDF with placebo reported HIV incidence. The meta-analysis of these two RCTs (Peterson 2007; Baeten 2012) demonstrated that high-risk individuals treated with TDF showed lower HIV incidence than those on placebo (RRRMRE 0.33; 95% 0.20 to 0.55; 4027 participants). There was no significant statistical heterogeneity ($I^2 = 0\%$, $p=0.97$) (Figure 5; Analysis 2.1).

![Figure 4. Forest plot of comparison: 1 TDF+ FTC vs placebo, outcome: 1.1 HIV infection (by risk group).](image-url)
In gender pre-specified subgroup meta-analysis (Baeten 2012; Thigpen 2012), TDF-FTC was statistically significantly more efficacious than placebo in reducing HIV infection in both men and women. However, TDF-FTC was more efficacious in men (RR\text{MH RE} 0.17; 95% CI 0.07 to 0.41) than in women (RR\text{MH RE} 0.40; 95% CI 0.20 to 0.71) (Figure 6). However, this gender differential in effectiveness of TDF-FTC did not reach statistical significant level (p-value for interaction = 0.10).
A comparison of TDF-FTC versus TDF alone did not show any statistically significant difference in the incidence of HIV infection (RR 0.72; 95% CI 0.36 to 1.47).

Adherence
In Baeten 2012, adherence, which was measured by monthly pill count of unused study product, was similar (97%) in all the study arms. In Van Damme 2012, reported adherence was 95% in both study arms; adherence based on pills count was 86% in the TDF-FTC group and 89% in the placebo group. However, measurements of drug levels in study volunteers’ blood was significantly lower. Among participants in the TDF-FTC group who remained uninfected, 38% had detectable drug levels in their blood. Among those who were infected, detectable drug levels was found in only 21%. The reported adherence in Grant 2010 was found to be similar between the FTC-TDF and placebo arm. However, the exposure to TDF-FTC measured objectively in the intervention arm was substantially lower than reported. TDF-FTC was detected in 51% of participants who remained HIV negative and only in 9% of those who became infected. There was a similar pattern of adherence in the group receiving a daily regimen of TDF-FTC and those receiving TDF-FTC intermittently in Mutua 2010. Thigpen 2012, also reported similar levels of adherence between the TDF-FTC and placebo group (84.1% and 83.7 percent respectively). Peterson 2007 did not provide details on the rates of adherence in each of the two study arms.

Sexual behaviour (post hoc)
Baeten 2012 and Grant 2010 reported similar sexual practices across the groups. There were no significant differences in the number of subjects with syphilis, gonorrhoea, chlamydia, genital warts or genital ulcers (Grant 2010). In Peterson 2007 during screening, participants reported an average of 12 coital acts per week with an average of 21 sexual partners in the previous 30 days. During follow-up, participants reported an average of 15 coital acts per week, with an average of 14 sexual partners in the previous 30 days. Self-reported condom use increased from 52% at screening to an average of 92% at the follow-up period. The authors did not provide details on the sexual behaviour in each of the study arms.

Adverse Events
Baeten 2012; Grant 2010; and Thigpen 2012 reported similar rates of serious adverse events between the TDF-FTC group and placebo group (RR$_{MHR}$ 1.00; 95% CI 0.83 to 1.19; 6862 participants) (Figure 7; Analysis 1.3. Also, Baeten 2012 did not find any significant difference in the rates of adverse events between the TDF group and placebo group (RR$_{MHR}$ 1.03; 95% CI 0.79 to 1.33; 3168 participants) (Figure 8: Analysis 2.2). A comparison of TDF-FTC versus TDF alone did not show any statistically significant difference in the incidence of severe adverse events (RR 0.99; 95% CI 0.77 to 1.29).

![Figure 7. Forest plot of comparison: 2 TDF-FTC vs placebo, outcome: 2.2 Adverse events.](image)

![Figure 8. Forest plot of comparison: 1 TDF vs placebo, outcome: 1.2 Adverse events.](image)
In Grant 2010 a small number of participants in the TDF-FTC group developed renal insufficiency which was reversible on discontinuation of the drug. Van Damme 2012 found mild-to-moderate increases in alanine amino transferase (ALT) and aspartate aminotransferase (AST) were more common in the TDF-FTC group. However, only the difference in ALT measurements was statistically significant. There were no differences in creatinine or phosphorous levels were seen between the two study groups. Peterson 2007 reported 22 serious adverse events (9 in the TDF group and 13 in the placebo group) in 17 participants. None of the serious adverse events were considered related to study drug. Mutua 2010 did not find any drug-related severe adverse events and no significant renal dysfunction. Among those on the daily regimen, there was a total of 203 adverse events out of which 76% are judged to be unrelated to the study medication. A similar pattern was observed among those on the intermittent regimen with a total of 152 adverse events out of which 84% are unrelated to the study medication.

All the studies reported significantly higher rates of nausea and vomiting in the TDF-FTC group compared to placebo.
### ADDITIONAL SUMMARY OF FINDINGS

**Explanation**

Tenofovir compared to placebo for preventing HIV in high-risk individuals

**Patient or population:** High-risk individuals (including serodiscordant couples, men who have sex with men and sex workers)

**Settings:** High, middle and low income settings

**Intervention:** Oral Tenofovir

**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>Study population</td>
<td>RR 0.33 (0.20 to 0.55)</td>
<td>4027</td>
<td>⊕⊕⊕</td>
<td>Moderate¹</td>
</tr>
<tr>
<td></td>
<td>Placebo TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 per 1000 9 per 1000 (6 to 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Study population</td>
<td>RR 1.03 (0.79 to 1.33)</td>
<td>3168</td>
<td>⊕⊕⊕⊕</td>
<td>Moderate¹</td>
</tr>
<tr>
<td></td>
<td>66 per 1000 68 per 1000 (52 to 88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRAD Working Group grades of evidence

- **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** We are very uncertain about the estimate.

¹ We downgraded the quality of evidence by one level on account of instability of results since there are fewer than 200 events per arm.
DISCUSSION

Summary of main results

Overall, results from four trials (Baeten 2012; Van Damme 2012; Grant 2010; Thigpen 2012) that compared TDF-FTC versus placebo shows a reduction in the risk of acquiring HIV infection by about 51%. Of these 4 trials, Van Damme 2012 failed to demonstrate a reduction in the risk of HIV infection with the use of TDF-FTC, possibly due to inadequate adherence to the trial medications by the participants. In the other two trials (Peterson 2007; Baeten 2012) that compared TDF only versus placebo, there was a significant reduction in the risk of acquiring HIV infection by about 67%.

The rate of adherence was found to be similar between the TDF-FTC vs. placebo arm and TDF vs. placebo. However, measurements of drug levels in some study volunteers suggested that the level of adherence was lower than reported by the participants. Sexual behaviour was similar across the study arms, and there was no evidence of potential risk compensation or behavioural disinhibition. The studies also reported similar rates of serious adverse events. However, a small number of participants in the TDF-FTC group were found to have developed renal insufficiency which was reversible on discontinuation of the drug. This raises some long term safety concerns.

Overall completeness and applicability of evidence

We included all studies that met the inclusion criteria for this review. The trials included participants from different risk groups (men who have sex with men, serodiscordant couples, female sex workers and other high-risk men and women). None of the completed studies included injection drug users. The studies were conducted in different settings: including high, middle and low-income countries. Therefore the findings from this review are applicable to various settings.

Quality of the evidence

The quality of the evidence was assessed using the GRADE methodology, and the basis for the judgements is presented in two ‘Summary of findings’ tables (Summary of findings for the main comparison; Summary of findings 2). The overall quality of evidence on the effectiveness of PrEP for preventing HIV in high-risk individuals can be described as moderate quality. We downgraded the quality of evidence by one level on account of instability of results since there are fewer than 200 events per arm.

Potential biases in the review process

We conducted a comprehensive search to ensure that all relevant completed or ongoing studies were identified. There was no language restriction. We also reduced potential bias in the conduct of this review by having two of the authors independently scan through the search output, extract data, and assess the methodological quality of each study.

AUTHORS’ CONCLUSIONS

Implications for practice

Findings from this review suggests that the use of oral TDF alone or a combination of TDF and FTC reduces the risk of acquiring HIV in high risk individuals. The use of PrEP with other existing HIV prevention strategies will provide the greatest protection to individuals at risk.

Many studies have examined the cost-effectiveness of PrEP. A mathematical modelling study on the cost-effectiveness of PrEP concluded that PrEP could prevent a significant number of infections among high-risk men who have sex with men and be cost effective (Desai 2008). Another mathematical modelling study that evaluated the cost-effectiveness of PrEP in South Africa showed that the cost-effectiveness of PrEP relative to ART decreases rapidly as ART coverage increases beyond three times its coverage in 2010 (Pretorius 2010).

Implications for research

In the search for highly reliable HIV prevention strategies, it is important to determine how PrEP can best be combined with existing programs, as no strategy is likely to be 100% effective. The efficacy of PrEP for prevention of HIV in high-risk individuals has been demonstrated, but additional research is needed to answer the following questions: What would be the best method for administering PrEP: daily versus intermittent dosing? How would adherence affect the efficacy of PrEP, and what are the determinants of PrEP adherence in people at high risk of infection? What will be the effect of PrEP on resistance in individuals who become infected and the possible transmission of drug-resistant virus? What are the long term effects of using PrEP? There is also a need for research on the feasibility of implementing PrEP into different contexts, including resource-constrained settings where ART treatment coverage is inadequate. Another important issue that will need to be addressed will be the long-term cost effectiveness of PrEP.

ACKNOWLEDGEMENTS

Charles I. Okwundu was awarded a Reviews for Africa Programme Fellowship (www.mrc.ac.za/cochrane/rap.htm) funded by the Nuffield Commonwealth Programme through The Nuffield Foundation.
Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

References to studies included in this review

Baeten 2012 [published and unpublished data]

Grant 2010 [published data only]

Mutua 2010 [published and unpublished data]

Peterson 2007 [published data only]

Thigpen 2012 [published and unpublished data]

Van Damme 2012 [published and unpublished data]

References to studies excluded from this review

Brooks 2003 [published data only]

References to ongoing studies

Chirenje 2012 [unpublished data only]

Chirenje 2012 [unpublished data only]

Choopanya 2010 [unpublished data only]

Grant 2012 [unpublished data only]

Molina 2012 [published data only]

NIAID 2012 [unpublished data only]

Paxton 2007 [published data only]

Additional references

Abdool Karim 2010

AFAO 2005

AIDS 2005

Anglemyer 2011
Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

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### Characteristics of included studies

**[ordered by study ID]**

**Baeten 2012**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized controlled trial</th>
</tr>
</thead>
</table>
| Participants | HIV-1 uninfected individuals within HIV-1 discordant partnerships (men and women age 18 Years to 69 Years)  
Inclusion Criteria for HIV-1 uninfected partner:  
- Partner within an HIV-1 discordant heterosexual relationship  
- One partner meets study eligibility for HIV-1 uninfected participant and the other partner meets study eligibility criteria for HIV-1 infected participant  
- Plan to remain in the relationship for the duration of the study period  
- Adequate renal, hepatic & hematologic function  
- Negative Hepatitis B surface antigen test  
- Willing and able to provide written informed consent & locator information  
Exclusion Criteria for HIV-1 uninfected partner:  
- Current pregnancy, or planning to become pregnant during the study period  
- Currently breastfeeding  
- Concurrent enrolment in another HIV-1 vaccine or prevention trial  
- Receiving ongoing antiretroviral therapy  
- Repeated positive urine dipstick tests for glycosuria or proteinuria  
- Active and serious infections  
- History of pathological bone fractures not related to trauma  
Inclusion Criteria for HIV-1 infected partner:  
- Partner within an HIV-1 discordant heterosexual relationship  
- One partner meets study eligibility for HIV-1 uninfected study participant and the other partner meets study eligibility criteria for HIV-1 infected participant  
- HIV-1 infected based on positive EIA  
- No history of any clinical AIDS-defining diagnoses  
- Plan to remain in the relationship for the duration of the study period  
- Willing and able to provide written informed consent & locator information  
Exclusion Criteria for HIV-1 infected partner:  
- Current use of antiretroviral therapy  
- Concurrent enrolment in another HIV-1 treatment trial |

| Interventions | Daily Tenofovir Disoproxil Fumarate 300 mg vs. placebo  
Daily Tenofovir Disoproxil Fumarate 300 mg + Emtricitabine 200 mg vs. placebo |

| Outcomes | Primary Outcome Measures:  
- Efficacy of once daily PrEP in preventing HIV-1 acquisition among uninfected heterosexual HIV-1 discordant couples.  
- Safety of daily TDF or FTC/TDF among HIV-1 uninfected individuals randomised to TDF or FTC/TDF to those randomised to placebo.  
Secondary Outcome Measures:  
- Reported risk behaviours, STI prevalence, pill counts and reported adherence.  
- HIV-1 drug resistance, plasma HIV-1 RNA levels and CD4 T cell counts among HIV-1 seroconverters.  
- Congenital abnormalities, growth and development among infants born to female HIV-1-infected mothers who were taking PrEP and those who were not, and among infants born to discordant partners during the randomisation period. |

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*Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)*  
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Baeten 2012** *(Continued)*

<table>
<thead>
<tr>
<th>Notes</th>
<th>The study was conducted in Kenya and Uganda</th>
</tr>
</thead>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>HIV-1 uninfected partners were assigned in a 1:1:1 ratio to one of three study arms: once-daily TDF, TDF-FTC, or placebo, using a fixed-size block randomisation, stratified by site</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A telephonic interactive voice response system was used to assign study drug kits. The investigators, except for statistical staff at the central coordinating center, remained unaware of the randomisation assignments</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>There was blinding of participants and investigators. Active and placebo TDF were indistinguishable, as were active and placebo TDF-FTC</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Retention rates were similar in the different study arms</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No evidence of selective outcome reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential sources of bias identified</td>
</tr>
</tbody>
</table>

**Grant 2010**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Men who have sex with men</td>
</tr>
<tr>
<td></td>
<td>Inclusion Criteria:</td>
</tr>
<tr>
<td></td>
<td>• Male sex (at birth)</td>
</tr>
<tr>
<td></td>
<td>• HIV uninfected</td>
</tr>
<tr>
<td></td>
<td>• Age having reached the local age of consent</td>
</tr>
<tr>
<td></td>
<td>• High risk for HIV infection including any of the following: 1) No condom use during anal intercourse with a male HIV-uninfected partner or a male partner of unknown HIV status during the last 6 months; (2) anal intercourse with more than 3 male sex partners during the last 6 months; (3) exchange of money, gifts, shelter, or drugs for anal sex with a male partner during the last 6 months; (4) sex with a male partner and STI diagnosis during the last 6 months or at screening, or (5) sexual partner of an HIV-infected man with whom condoms are not consistently used in the last 6 months.</td>
</tr>
<tr>
<td></td>
<td>• Able to provide a street address of residence for themselves and one personal contact who would know their whereabouts during the study period</td>
</tr>
<tr>
<td></td>
<td>• Healthy enough to work, as indicated by score of 80 or greater on the Karnofsky</td>
</tr>
</tbody>
</table>
### Inclusion Criteria for Open-Label Extension:

- Participated in a randomised, placebo-controlled, PrEP trial
- Has been unblinded
- Has provided informed consent

### Exclusion Criteria:

- Previously diagnosed active and serious infections, including tuberculosis infection, osteomyelitis, or infections requiring parenteral antibiotic therapy
- Active clinically significant medical problems including heart disease (e.g., symptoms of ischemia, congestive heart failure, arrhythmia), lung disease (steroid-dependent chronic obstructive pulmonary disease), diabetes requiring hypoglycemic medication, or previously diagnosed cancer expected to require further treatment
- Acute HBV infection at the screening visit or presence of treatment indications for hepatitis B based on local practice standards; or clinical signs of hepatic cirrhosis
- History of pathological bone fractures not related to trauma
- Receiving ongoing therapy with certain HIV/AIDS-related medications or other medications as determined by the investigator
- Definitely or possibly received an anti-HIV vaccine while participating in a blinded clinical trial
- Current alcohol or drug use that, in the opinion of the investigator, may interfere with the study
- Current participation in a clinical trial or cohort study other than sub-studies of this protocol
- Any condition at enrolment that, in the opinion of the investigator, would make participation in the study unsafe or would interfere with the study
- Sites may utilize additional criteria that restrict enrolment to a subset of people who meet the protocol-defined enrolment criteria.

### Exclusion Criteria for Open-Label Extension:

- Site leadership believes participant will have difficulty completing requirements

### Interventions

| Daily Tenofovir Disoproxil Fumarate 300 mg + Emtricitabine 200 mg vs. placebo |

### Outcomes

<table>
<thead>
<tr>
<th>Primary Outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HIV seroconversion</td>
</tr>
<tr>
<td>Safety endpoints, including Grade 1 or higher creatinine toxicity; Grade 3 or higher phosphorous toxicity; Grade 2, 3, or 4 laboratory adverse events; or Grade 2, 3, or 4 clinical adverse events; or HIV seroconversion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcome Measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis flares among hepatitis B virus (HBV) infected persons during and after chemoprophylaxis</td>
</tr>
<tr>
<td>Changes in bone mineral density, body fat distribution, or fasting triglyceride and cholesterol levels</td>
</tr>
<tr>
<td>Among HIV infected participants: viral load, drug resistance, and CD4 count</td>
</tr>
<tr>
<td>Proportion of missed doses by pill count and by estimate during CASI interview</td>
</tr>
</tbody>
</table>
Grant 2010  

(Continued)

<table>
<thead>
<tr>
<th>Risk behavior, including number of sexual partners with HIV positive or unknown status, total number of sexual partners, and condom use before, during, and after use of study medication</th>
<th>Notes</th>
<th>This is a multinational trial conducted in Peru, Ecuador, South Africa, Brazil, Thailand and the United States</th>
</tr>
</thead>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Subject codes were randomly assigned in blocks of 10, stratified according to site</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The method used for allocation concealment is not described</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>There was blinding of participants and investigators</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Incomplete outcome data were properly addressed</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No evidence of selective outcome reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential sources of bias identified</td>
</tr>
</tbody>
</table>

Mutua 2010

Methods  
Randomized controlled trial

Participants  
HIV negative men and women aged 18 to 49 Years  
Inclusion Criteria:  
- Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study  
- Has understood the information provided and has provided written informed consent before any study-related procedures are performed  
- Willing to undergo HIV testing, STI screening, HIV counselling and receive HIV and STI test results  
- At risk for HIV infection as defined by at least one of the following:Current sexually-transmitted infection (STI) or STI in the previous 3 monthsIn the past 3 months had multiple episodes of unprotected vaginal sexIn the past 3 months had multiple episodes of unprotected anal sexIn the past 3 months engaged in sex work for money or drugs  
- If a female of childbearing potential (i.e., not post-menopausal or surgically sterile), using an effective method of non-barrier contraception (hormonal antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review) Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
contraceptive; intrauterine device (IUD); surgical sterility) from 7 days prior to randomisation until the end of the study. All female volunteers must be willing to undergo urine pregnancy tests.

**Exclusion Criteria:**
- Confirmed HIV-1 or HIV-2 infection
- Any clinically significant acute or chronic medical condition that is considered progressive or in the opinion of the investigator would make the volunteer unsuitable for the study, including severe infections requiring treatment such as tuberculosis, and alcohol or drug abuse
- Any of the following abnormal laboratory parameters:
  - Haemoglobin <9.0 g/dL
  - Creatinine clearance <80mL/min, as calculated by Cockcroft-Gault equation
  - AST: >2.5 x ULN
  - ALT: >2.5 x ULN
  - Total bilirubin >1.5 x ULN
  - Serum phosphorus <2.4 mg/dL
  - Urinalysis: Two abnormal dipsticks showing any of the following:
    - Blood = 2+ or more (not due to menses)
    - Protein = 1+ or more
    - Leucocytes = 2+ or more
    - Glucose = 1+ or more
- Confirmed diagnosis of chronic hepatitis B infection (HBsAg positive)
- If female, pregnant or planning a pregnancy within 4 months after enrolment or lactating
- Participation in another clinical study of an investigational product currently, within the 3 months prior to enrolment or expected participation during this study

### Interventions

| Daily vs intermittent Tenofovir Disoproxil Fumarate plus Emtricitabine (FTC/TDF) |

### Outcomes

**Primary Outcome Measures:**
- Safety and tolerability: The proportion of volunteers with moderate and greater severity clinical adverse events; mild, moderate and greater severity of renal toxicities, and other moderate and severe laboratory abnormalities.
- Acceptability: The proportion of volunteers who report willingness to use the study regimen
- Intracellular drug concentrations: The mean intracellular drug concentration for each group assigned to FTC/TDF
- Adherence: Proportion of volunteers who took, by MEMS data, at least 80% of expected doses of the IP; Proportion of volunteers assigned to FTC/TDF who have detectable drug plasma levels within 48 hrs of use.

**Behavioral:** Reported number of steady and casual sex partners; Frequency of unprotected vaginal and/or anal intercourse; Substance use prior to or during sex.

**Secondary Outcome Measures:**
- Proportion of volunteers who report somewhat high or high levels of burden in using electronic medication monitoring to measure adherence, and using cell phone communication to measure sexual activity
- The proportion of study days with missing SMS sexual activity data
- The proportion of volunteers who report sharing medications
- The proportion of volunteers assigned to placebo who have detectable intracellular drug levels
- The proportion of volunteers with HIV-specific immune responses as measured by analysis of cellular or humoral immune response, or changes in gene regulation as measured by microarray or proteomic techniques.

### Notes

The study was conducted in Kenya.
### Mutua 2010 (Continued)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>A random allocation sequence was generated by an external data coordinating centre. Investigators at the study sites enrolled participants via an electronic enrolment system where allocation codes were assigned consecutively to eligible volunteers at the time of first dispensation of study drug</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation was done by an external centre.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>There was blinding of participants and investigators to the study medications. However, the allocation to daily or intermittent dosing was not blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>There was no loss to follow up.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No evidence of selective outcome reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential source of bias</td>
</tr>
</tbody>
</table>

### Peterson 2007

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women aged 18 to 35 years</td>
</tr>
<tr>
<td></td>
<td>Inclusion Criteria:</td>
</tr>
<tr>
<td></td>
<td>* HIV seronegative</td>
</tr>
<tr>
<td></td>
<td>* Willing and able to give informed consent</td>
</tr>
<tr>
<td></td>
<td>* 18 years to 35 years old, inclusive</td>
</tr>
<tr>
<td></td>
<td>* Sexually active (on average, coitus 3 times per week)</td>
</tr>
<tr>
<td></td>
<td>* Have had more than three sexual partners in the last month</td>
</tr>
<tr>
<td></td>
<td>* Willing to use study product as directed</td>
</tr>
<tr>
<td></td>
<td>* Willing to adhere to follow-up schedule</td>
</tr>
<tr>
<td></td>
<td>* Willing to participate in the study for up to 12 months</td>
</tr>
<tr>
<td></td>
<td>* Not pregnant, breast feeding, or desiring a pregnancy during the 12 months of participation</td>
</tr>
<tr>
<td></td>
<td>* Have adequate renal function (serum creatinine &lt; 1.5 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>* Have adequate liver function (hepatic transaminases [ALT and AST] &lt; 43 U/L)</td>
</tr>
<tr>
<td></td>
<td>* Have adequate serum phosphorus (greater than or equal to 2.2 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>* In general good health</td>
</tr>
<tr>
<td>Interventions</td>
<td>Daily 300 mg tenofovir disoproxil fumarate versus placebo</td>
</tr>
</tbody>
</table>
### Peterson 2007

**Outcomes**

Primary Outcome Measures:
- Effectiveness endpoint: conversion for antibodies to HIV 1 or 2
- Laboratory safety endpoints including serum creatinine and phosphorus for kidney function, and AST and ALT for hepatic function.
- Reported adverse events

**Notes**

This is a multinational study conducted in Ghana, Cameroon and Nigeria

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>A random allocation sequence was generated using a computer random number generator</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation was concealed by the use of sealed opaque envelopes. The randomisation envelopes were maintained in a secure office. They were not available to the study counsellors until the immediate moment of randomisation</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>Placebo tablets were made to match the TDF tablets, and contained denatonium benzoate to provide a bitter taste to resemble the active tablets</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Some data were discarded (Nigeria-safety data)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No evidence of selective outcome reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>There was premature stoppage of the trial at the Cameroon and Nigeria sites</td>
</tr>
</tbody>
</table>

### Thigpen 2012

**Methods**

Randomized controlled trial

**Participants**

1200 HIV uninfected, sexually active healthy male and female volunteers

Inclusion Criteria:
- citizen of Botswana 18-29 years old
- sexually active
- HIV uninfected
- Hepatitis B and C uninfected
- Calculated creatinine clearance $\geq 60$ mL/min
- hemoglobin $\geq 8$ gm/dL
- ALT and AST $\leq 2x$ ULN
- total bilirubin $\leq 1.5$ mg/dL
- total serum amylase $\leq 1.5x$ ULN
• Serum phosphorus >= 2.2 mg/dL
• willing to use hormonal contraception (females)
• living within 1 hours travel of study clinic
• pass comprehension test
• willing and able to give informed consent

Exclusion Criteria:
• 18-20 without parent/guardian consent
• history of significant renal or bone disease
• any chronic illness requiring ongoing prescription medication
• pregnant or breastfeeding
• planning to move away from site in the next year
• participating in another HIV prevention or vaccine safety trial
• any other clinical condition or prior therapy that, in the opinion of the study physician, would make the volunteer unsuitable for the study or unable to comply with the dosing requirements

Interventions

Tenofovir Disoproxil Fumarate 300 mg + Emtricitabine 200 mg daily

Outcomes

Primary Outcome Measures:
• Adverse drug reactions
• HIV incidence in the tenofovir/emtricitabine and placebo arms

Secondary Outcome Measures:
• Changes in levels of unprotected sex during the trial;
• Adherence to medication;
• Antiretroviral (ARV) resistance patterns in seroconverters;
• Viral set point in seroconverters

Notes

The study was conducted in Botswana

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Participants were randomised in a 1:1 ratio using random, permuted blocks of six, stratified by site and gender</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>The randomisation was done randomly centrally</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>Neither researchers nor participants knew an individual’s group assignment</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Similar rates of attrition in both groups and all participants were accounted for</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No evidence of selective outcome reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>We did not identify any other potential source of bias</td>
</tr>
<tr>
<td>Methods</td>
<td>Randomized controlled trial</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| **Participants** | HIV-antibody-negative women between the ages of 18-35 who were at risk of HIV acquisition through sexual intercourse  
Inclusion Criteria:  
• Willing and able to provide written informed consent to be screened for and to participate in the trial  
• Able to answer a percentage of informed consent screening (75%) and enrolment (100%) comprehension quiz questions correctly  
• Between 18-35 years old, inclusive  
• At higher risk of becoming HIV infected  
• Have a final negative result according to the site-specific screening HIV testing algorithm and a final negative result at enrolment according to the study HIV testing algorithm  
• Willing to participate in all aspects of the study and to comply with study procedures, for up to 60 weeks, including:  
  • Not intending to relocate out of the area for the duration of the study participation and does not have a job or other obligations that may require long absences from the area ( > 1 month at a time)  
  • In general good health and have no condition (social or medical) which, in the opinion of the Site Investigator, would make study participation unsafe or complicate data interpretation  
  • Not pregnant or breastfeeding, and does not anticipate a desire for pregnancy during the 52 weeks of on-product participation  
  • Not received or receiving an experimental HIV vaccine, participating in another HIV prevention study or participating in any other clinical trial with a biomedical intervention  
  • No clinical signs of liver disease (e.g., ascites, spider angiomata, hepatomegaly, jaundice)  
  • No definite evidence of glycosuria or proteinuria (i.e., no repeated positive [ ≥ 1 ] urine dipstick). If a urine dipstick is positive for either glucose and/or protein at the first test, a second urine sample will be tested.  
  • No history of pathological bone fractures  
  • No history of adverse reaction to latex  
  • Not taking any of the following medications: nephrotoxic agents; aminoglycoside antibiotics (including gentamicin); intravenous (IV) amphotericin B; cidofovir; cisplatin; foscarnet; IV pentamidine; oral or IV vancomycin; oral or IV gancyclovir; other agents with significant nephrotoxic potential; drugs that slow renal excretion; probenecid; immune system modulators; systemic chemotherapeutic agents (i.e. cancer treatment medications); systemic corticosteroids; interleukin-2 (IL-2); immunomodulators; interferon (alpha, beta, or gamma); other antiretrovirals (including nucleoside analogs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents) |
| **Interventions** | Daily Tenofovir Disoproxil Fumarate 300 mg + Emtricitabine 200 mg vs placebo |
| **Outcomes** | Primary Outcome Measures:  
• Combined incidence of HIV-1 and HIV-2 infection  
• Incidence of confirmed Grade 2 or higher serum creatinine toxicity, and Grade 3 or higher AST, ALT, or phosphorus toxicity during and 4 weeks after study product |
administration

- Frequency and nature of adverse events (AEs) during and within 4 weeks after study product administration

Secondary Outcome Measures:

- Viral load and CD4+ T cell counts at the time of HIV diagnosis and at 4, 8, 12, 16, 24, 36 and 52 weeks later
- FTC and/or tenofovir resistance at the time of HIV diagnosis and 4 weeks later.
- Incidence of pregnancy loss, prematurity, low birth weight, and congenital abnormalities
- Pill counts and participant report of adherence to once-daily pill taking
- Participant report of the number of sexual partners and frequency of unprotected sexual acts over time
- Participant report of sexual behaviours and sex partner characteristics by participants who seroconvert and HIV negative participants

Notes

The study was conducted in Kenya, South Africa, Tanzania and Zimbabwe

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>The authors described the use of block randomization</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Envelopes were used to conceal the assignment of participants</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>There was blinding of participants and investigators</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Similar rates of attrition in both groups and all participants were accounted for</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No evidence of selective outcome reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential sources of bias identified</td>
</tr>
</tbody>
</table>

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brooks 2003</td>
<td>Phase trial with no control group</td>
</tr>
</tbody>
</table>
### Characteristics of ongoing studies  
*ordered by study ID*

#### Chirenje 2012

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and Effectiveness of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate, and Emtricitabine/Tenofovir Disoproxil Fumarate Tablets in Preventing HIV in Women. MTN-003 (VOICE)</td>
<td>Sexually active women in South Africa, Uganda and Zimbabwe</td>
</tr>
<tr>
<td>Methods</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td><strong>Inclusion Criteria:</strong></td>
<td></td>
</tr>
<tr>
<td>• Willing to provide adequate locator information</td>
<td></td>
</tr>
<tr>
<td>• Sexually active, defined as having vaginal intercourse at least once in the 3 months prior to screening</td>
<td></td>
</tr>
<tr>
<td>• Agree to not participate in other research studies involving drugs, medical devices, or vaginal products for duration of study</td>
<td></td>
</tr>
<tr>
<td>• Agree to use effective method of contraception. More information on this criterion can be found in the protocol.</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion Criteria:</strong></td>
<td></td>
</tr>
<tr>
<td>• HIV infected</td>
<td></td>
</tr>
<tr>
<td>• Known adverse reaction to any of the study products</td>
<td></td>
</tr>
<tr>
<td>• Known adverse reaction to latex</td>
<td></td>
</tr>
<tr>
<td>• Pathologic bone fracture not related to trauma</td>
<td></td>
</tr>
<tr>
<td>• Non-therapeutic injection drug use in the 12 months prior to screening</td>
<td></td>
</tr>
<tr>
<td>• Post-exposure prophylaxis for HIV exposure within 6 months prior to enrolment</td>
<td></td>
</tr>
<tr>
<td>• Last pregnancy outcome 42 days or less prior to enrolment</td>
<td></td>
</tr>
<tr>
<td>• Gynecologic or genital procedure 42 days or less prior to enrolment</td>
<td></td>
</tr>
<tr>
<td>• Participation in any other research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrolment</td>
<td></td>
</tr>
<tr>
<td>• Currently using spermicide, interferon or interleukin therapy, or certain medications. More information on this criterion can be found in the protocol.</td>
<td></td>
</tr>
<tr>
<td>• Any significant uncontrolled active or chronic disease. More information on this criterion can be found in the protocol.</td>
<td></td>
</tr>
<tr>
<td>• Certain abnormal laboratory values. More information on this criterion can be found in the protocol.</td>
<td></td>
</tr>
<tr>
<td>• Intends to become pregnant in the 24 months after enrolment</td>
<td></td>
</tr>
<tr>
<td>• Plans to relocate or travel away from the study site for more than 8 consecutive weeks in the 24 months after enrolment</td>
<td></td>
</tr>
<tr>
<td>• Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td>• Pelvic inflammatory disease, an STI, or reproductive tract infection requiring treatment</td>
<td></td>
</tr>
<tr>
<td>• Grade 2 or higher pelvic exam finding</td>
<td></td>
</tr>
<tr>
<td>• Any condition that, in the opinion of the investigator, would interfere with the study</td>
<td></td>
</tr>
<tr>
<td>• Pregnant or breastfeeding</td>
<td></td>
</tr>
</tbody>
</table>

| Interventions                                                                 | 200 mg/300 mg tablet TDF-FTC versus placebo                                  |
|                                                                                | 300 mg tablet TDF versus placebo                                             |

| Outcomes                                                                      | Primary Outcome Measures:                                                    |
|                                                                              | • Effectiveness of oral TDF and oral FTC/TDF versus oral placebo measured by HIV seroconversion |
|                                                                              | Secondary Outcome Measures:                                                  |
|                                                                              | • Adherence                                                                  |
|                                                                              | • Change in sexual activity, condom use, and intravaginal practices           |
|                                                                              | • Frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using study product |
Chirenje 2012 (Continued)

- Reported HIV seroconversion, toxicity, viral resistance, cervicovaginal inflammation, or adverse events
- Incidence of HIV seroconversion in each study product group

Starting date
September 2009

Contact information
Zvavahera M. Chirenje, MD, FRCOG. UZ-UCSF Collaborative Research Programme. Jeanne Marrazzo, MD, MPH. University of Washington, Division of Allergy and Infectious Disease

Notes
ClinicalTrials.gov Identifier:

Choopanya 2010

Trial name or title
Bangkok Tenofovir Study

Methods
Randomised controlled trial

Participants
Injection drug users aged between 20 and 60 (both gender)

Inclusion Criteria:
- Report injection drug use in the 6 months before screening
- Possess a Thai National Identification Card
- Laboratory values as follows within 2 weeks before enrolment:
  - HIV oral fluid test non-reactive at screening and pre-enrollment visits
  - Hemoglobin 9 gm/dL
  - ALT and AST 2.5 x upper limit of normal (ULN)
  - Total bilirubin 1.5 mg/dL
  - Serum amylase 1.5 x ULN
  - Serum phosphorus 2.2 mg/dL
  - No evidence of current or chronic Hepatitis B infection by serology
  - Calculated creatinine clearance 60 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min = Male: (140 - age in years) x (wt in kg)/72 x (serum creatinine in mg/dL) Female: (140 - age in years) x (wt in kg) x 0.85/72 x (serum creatinine in mg/dL)
  - Willing to abstain from sexual intercourse or use effective contraception during the trial (oral, injection, or barrier), for women
  - Willing and able to provide informed consent for study participation
  - Available and committed to DOT or monthly follow-up for at least 12 months

Exclusion Criteria:
- Clinic physicians will determine if a subject with chronic illness requiring prescription medication can not enroll (medication used for drug treatment is allowed)
- Positive urine pregnancy test
- Breastfeeding
- History of significant renal, liver, or bone disease
- Any other clinical condition or prior therapy that, in the opinion of the clinic physician, would make the subject unsuitable for the study or unable to comply with the dosing requirements
- Concurrent participation in any other HIV prevention trial or drug/vaccine safety trial. AIDSVAX B/E HIV vaccine trial (CDC protocol #2076) participants and Extension Study (CDC protocol #3750) participants may be screened for enrolment in the Bangkok Tenofovir Study.

Interventions
Oral tenofovir 300 mg versus placebo
### Choopanya 2010

#### Outcomes

**Primary Outcome Measures:**
- Adverse events
- Rates of HIV seroconversion
- Frequency of grade 3 or 4 renal or hepatic function laboratory toxicities or clinical toxicities
- Frequency of adverse clinical events in tenofovir and placebo arm

**Secondary Outcome Measures:**
- Rates of injecting and needle sharing
- Adherence to study drug/placebo
- HIV viral load and CD4 counts
- Antiretroviral resistance
- Genetic characteristics of infecting
- The number of unprotected sexual acts over the course of the trial
- Number of reported sexual partners over the course of the trial
- Proportional use of condoms during sexual intercourse

#### Starting date

**June 2005**

#### Contact information

Principal Investigator: Kachit Choopanya, Bangkok Tenofovir Study Group
Study director: Michael T Martin, Centers for Disease Control and Prevention

#### Notes

Study location: Bangkok

---

### Grant 2012

**Trial name or title**

Use of Emtricitabine and Tenofovir Disoproxil Fumarate for Pre-Exposure Prophylaxis (ADAPT)

**Methods**

Randomised controlled trial (open label)

**Participants**

Men and women aged 18 years and older

- **Inclusion Criteria:**
  - Literacy in one of the study languages (Thai, Xhosa and/or English)
  - Able to provide written informed consent
  - Able to provide weekly telephonic updates
  - Certain lab valued within 70 days of enrolment
  - Willing and able to provide adequate locator information

- **Inclusion Criteria for Men Who Have Sex With Men (MSM):**
  - Male at birth
  - Reporting anal intercourse with at least one man in the past 6 months
  - Presence of one or more of the following risk factors for HIV acquisition in the past 6 months: sexual intercourse with more than one man; history of an acute sexually transmitted disease (STI); sex in exchange for money, goods, or favors; condom-less intercourse (oral, anal, or vaginal) with a partner known to be HIV-infected or of unknown HIV infection status according to self-report

- **Inclusion Criteria for Women Who Have Sex With Men (WSM):**
  - Female at birth or self identify as female
  - Not pregnant or breastfeeding
  - Not able to or not intending to become pregnant during the next year
  - If able to become pregnant, self reported use of an effective method of contraception at Enrollment,
and intending to use an effective method for the next 34 weeks

- One or more of the following risk factors for HIV acquisition in the past six months according to self report: sexual intercourse with more than one man; history of an acute STI; sex in exchange for money, goods or favors; condomless intercourse (oral, anal or vaginal) with a partner known to be HIV-infected or of unknown HIV infection status

Exclusion Criteria:

- Proteinuria 2+ or greater at screening
- Glucosuria 2+ or greater at screening
- Serious and active medical or mental illness
- One or both HIV rapid tests is reactive at screening or enrolment, regardless of subsequent HIV diagnostic test results
- Signs or symptoms suggestive of acute HIV infection
- Use of hypoglycemic agents for diabetes or agents with known nephrotoxic potential
- Serum phosphate level below site laboratory LLN (lower limit of normal)
- Current participation (or participation within three months of screening) in any HIV prevention study
- Previous or current participation in the active arm of an HIV vaccine trial
- Acute or chronic HBV infection
- Presence of a psychological or social condition or an addictive disorder that would preclude compliance with the protocol
- Any other reason or condition that in the opinion of the investigator would interfere with participation, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

Interventions

Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF): daily, time-based, and event-based dosing

Outcomes

Primary Outcome Measures:

- Proportion of sexual exposures covered by pre- and post-exposure dosing
- Minimum total number of pills needed for 100% coverage
- Total number of pills used over the follow-up period
- Self-reported side effect or symptom scores

Secondary Outcome Measures:

- Amount of tenofovir diphosphate (TFV-DP) in peripheral blood mononuclear cell (PBMC)
- Listing of adverse events (AEs) by grade
- Drug resistance test results and plasma HIV RNA levels among all participants who seroconvert while enrolled in the study
- Proportion of participants who self-report acceptability of assigned study arm, as collected on computer assisted self interview (CASI) assessment
- Perceptions of advantages and disadvantages of different regimens as reported by participants and clinical personnel
- Percentage of adherence and correctly timed adherence, measured by weekly interviews and electronic drug monitoring data
- Percentage of adherence, based on pill counts
- Proportion of participants who discontinue all pre-exposure prophylaxis (PrEP) use as assessed by self-report via CASI or weekly interviews
- Information related to PrEP use, motivation, and behavioral skills as assessed by self-report via CASI
- Frequency of unprotected sex acts as assessed via CASI
- Planning for sex as assessed via CASI
- Results of safer sex planning survey as assessed via CASI
- Perceived vulnerability as assessed via CASI
- PrEP optimism as assessed via CASI
**Grant 2012** (Continued)

| General optimism as assessed via CASI  |
| Demographic factors  |

**Starting date**  
September 2012

**Contact information**  
Study chair: Robert M. Grant, MD, MPH. University of California, San Francisco

**Notes**  
Study location: South Africa and Thailand

---

**Molina 2012**

| Trial name or title | On Demand Antiretroviral Pre-exposure Prophylaxis for HIV Infection in Men Who Have Sex With Men (IPERGAY) |
| Methods | Randomised controlled trial |
| Participants | Men who have sex with men aged 18 years and older  
Inclusion Criteria:  
- Age ≥ 18 years old  
- Male (or transgender) having sex with men  
- Not infected with HIV-1 or HIV-2  
- Elevated risk of HIV contamination : anal sexual relations with at least 2 different sexual partners within the past 6 months without the systematic use of a condom  
- Satisfactory kidney function with a clearance of more than 60 mL/min (Cockcroft formula)  
- ALT < 2.5 ULN  
- Neutrophil granulocytes ≥ 1 000/mm3, haemoglobin ≥ 10 g/dL, platelets ≥ 150 000/mm3  
- Negative HBs antigen and negative HCV serology (or negative HCV PCR if positive serology)  
- Agrees to be contacted personally, if possible by telephone, SMS or e-mail  
- Agrees to the constraints imposed by the trial (visits every 2 months)  
- Subjects enrolled in or a beneficiary of a Social Security program (State Medical Aid or AME is not a Social Security program).  
- Signature of the informed consent form.  
Exclusion Criteria:  
- Subject in a stable and exclusive relationship with a person  
- Systematic use of a condom during sexual relations  
- Expected to go abroad for more than 3 consecutive months or move expected to a city where the study is not being conducted.  
- Presence of significant glycosuria or proteinuria > 1+ in the urine dipstick, in the absence of infection.  
- Presence of significant haematuria or leukocyturia > 2+ in the urine dipstick, in the absence of infection.  
- History of chronic kidney disease, osteoporosis, osteopaenia  
- History of pathological bone fracture not related to trauma  
- Treatment with Interferon, Interleukin, corticosteroids or antiretrovirals  
- Treatment that could inhibit or compete with the tubular secretion of antiretrovirals  
- Treatment undergoing investigation  
- Intravenous toxicomania  
- Subject who is currently receiving or going to receive a potentially nephrotoxic treatment (long-term anti-inflammatory) |
### Interventions

- TDF-FTC versus placebo (taken at the time of intercourse)

### Outcomes

**Primary Outcome Measures:**
- Contamination with HIV-1 or -2

**Secondary Outcome Measures:**
- Evolution of sexual behavior and potential at-risk behavior
- Treatment adherence
- Incidence of hepatitis B
- Incidence of other sexually transmitted diseases
- Frequency of HIV resistance to antiretrovirals in HIV infected subjects
- Emtricitabine and tenofovir concentrations in plasma, saliva and rectal samples
- Costs evaluation

### Starting date

January 2012

### Contact information

Jean-Michel MOLINA, Hôpital Saint-Louis Paris FRANCE

### Notes

Study location: France

---

Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

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hepatitis B surface antigen (HBsAg) negative.

- No alcohol or substance use that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report or found upon medical history and examination or in available medical records)
- No medical condition that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report or found upon medical history and examination or in available medical records)
- Willing to undergo all required study procedures (including sexual assessment by CASI, use of the drug monitoring device, and SMS [i.e., texting])
- For the Tissue Subset: Willing to abstain from receptive anal intercourse and practices involving insertion of anything in the rectum (drug, enema, penis, or sex toy) for 48 hours prior to rectal biopsy and for 14 days post-biopsy to minimize risk of HIV-1 infection and bleeding complications after each flexible sigmoidoscopy procedure.

Exclusion Criteria:

- One or more reactive HIV test results at screening or enrolment, even if HIV infection is not confirmed
- Coenrollment in any other HIV interventional research study (provided by self-report or other available documentation) or prior enrolment and receipt of active arm (i.e., NOT a placebo) of an HIV vaccine trial (provided by available documentation)
- Use of ARV therapy (e.g., for post-exposure prophylaxis [PEP] or PrEP) in the 90 days prior to study entry
- Prior history of a gastrectomy, colostomy, ileostomy, or any other procedure altering the gastrointestinal tract or drug absorption (provided by self-report or obtained from medical history or records)
- Receipt of prohibited medications as described in the study drug package inserts or listed in the Study-Specific Populations (SSP) Manual (provided by self-report or obtained from medical history or medical records)
- Ongoing intravenous drug use: episodic use or any use in the past 3 months (as assessed by the study investigator)
- Known medical history of allergy to soy (soya or soybeans) or peanuts
- For the Tissue Subset: Abnormalities of the colorectal mucosa or significant colorectal symptom(s) that, in the opinion of the clinician, represent a contraindication to biopsy (including but not limited to presence of any unresolved injury, infectious or inflammatory condition of the local mucosa, and presence of symptomatic external hemorrhoids)
- For the Tissue Subset: Per participant report at screening, anticipated use and/or unwillingness to abstain from the following medications during the period of study participation: heparin, including lovenox; warfarin; plavix (clopidogrel bisulfate); rectally administered medications (including over-the-counter products); aspirin; non-steroidal anti-inflammatory drugs (NSAIDS); any other drugs that are associated with increased risk of bleeding following biopsy procedures
- Abnormal laboratory results for coagulation tests that may indicate an increased risk of bleeding (in the opinion of the investigators)
- Active untreated syphilis, gonorrhea, or chlamydia infection

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Four ARV regimens: maraviroc (MVC), MVC plus emtricitabine, MVC plus tenofovir disoproxil fumarate (TDF), and TDF plus FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Primary Outcome Measures:</td>
</tr>
<tr>
<td></td>
<td>- Safety as assessed by the occurrence of Grade 3 or higher adverse events</td>
</tr>
<tr>
<td></td>
<td>- Tolerability as assessed by time to permanent discontinuation of treatment</td>
</tr>
<tr>
<td></td>
<td>Secondary Outcome Measures:</td>
</tr>
<tr>
<td></td>
<td>- Safety as assessed by the occurrence of Grade 2 or higher adverse events</td>
</tr>
</tbody>
</table>
### NIAID 2012 (Continued)

| Changes in creatinine clearance and fractional excretion of phosphate |
| Changes in total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) (calculated or measured), and triglycerides |
| Pre-dose and post-dose concentrations of MVC, FTC, and tenofovir (TFV) in plasma |
| Pre-dose concentrations of drugs (MVC, FTC, TFV, and their phosphorylated derivatives), in plasma, peripheral blood mononuclear cells (PBMCs), and rectal samples |
| Pre-dose and post-dose concentrations of MVC, FTC, TFV, and tenofovir (TFV) in plasma (Drug Interaction Subset) |
| Changes in peripheral blood and gut-associated lymphoid tissue (GALT) T cell phenotype |
| Pre-dose and post-dose concentrations of MVC, FTC, and tenofovir (TFV) in plasma (Drug Interaction Subset) |
| Pre-dose concentrations of drugs (MVC, FTC, TFV, and their phosphorylated derivatives), in plasma, peripheral blood mononuclear cells (PBMCs), and rectal samples (Tissue Subset) |
| Self-reported adherence as assessed by proportion of daily doses taken, measured by electronic drug monitoring (EDM) |
| Proportion of doses taken as measured by EDM the day of and day prior to a sexual exposure as detected by SMS assessment |
| Selected drug concentration measurements in stored plasma samples |
| Self-reported quality of life indicators over time using a standardized assessment tool |
| Self-reported sexual behavior over time using a standardized assessment tool |

#### Starting date
2012

#### Contact information
National Institute of Allergy and Infectious Diseases (NIAID)

#### Notes
Study location: USA

---

### Paxton 2007

#### Trial name or title
Botswana TDF/FTC Oral HIV Prophylaxis Trial

#### Methods
Randomised controlled trial

#### Participants
Sexually-active men and women aged 18 to 29 years

**Inclusion Criteria:**
- citizen of Botswana 18-29 years old
- sexually active
- HIV uninfected
- Hepatitis B and C uninfected
- Calculated creatinine clearance >= 60 mL/min
- hemoglobin >= 8 gm/dL
- ALT and AST <= 2x ULN
- total bilirubin <= 1.5 mg/dL
- total serum amylase <= 1.5x ULN
- Serum phosphorus >= 2.2 mg/dL
- willing to use hormonal contraception (females)
- living within 1 hours travel of study clinic
- pass comprehension test
- willing and able to give informed consent

**Exclusion Criteria:**
- 18-20 without parent/guardian consent
- history of significant renal or bone disease
- any chronic illness requiring ongoing prescription medication
- pregnant or breastfeeding
- planning to move away from site in the next year
- participating in another HIV prevention or vaccine safety trial
- any other clinical condition or prior therapy that, in the opinion of the study physician, would make the volunteer unsuitable for the study or unable to comply with the dosing requirements

### Interventions

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Tenofovir Disoproxil Fumarate 300 mg + Emtricitabine 200 mg daily versus placebo</td>
</tr>
</tbody>
</table>

### Outcomes

**Primary Outcome Measures:**
- Adverse drug reactions in the tenofovir/emtricitabine and placebo arms;
- HIV incidence in the tenofovir/emtricitabine and placebo arms

**Secondary Outcome Measures:**
- Changes in levels of unprotected sex during the trial;
- Adherence to medication;
- Antiretroviral (ARV) resistance patterns in seroconverters;
- Viral set point in seroconverters

### Starting date

March 2007

### Contact information

Lynn A Paxton, MD, MPH. Centers for Disease Control and Prevention

### Notes

Study location: Botswana
## DATA AND ANALYSES

### Comparison 1. TDF+ FTC vs placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HIV infection (by risk group)</td>
<td>4</td>
<td>8918</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.49 [0.28, 0.85]</td>
</tr>
<tr>
<td>1.1 Heterosexual group</td>
<td>3</td>
<td>6419</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.46 [0.19, 1.10]</td>
</tr>
<tr>
<td>1.2 MSM group</td>
<td>1</td>
<td>2499</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.56 [0.38, 0.84]</td>
</tr>
<tr>
<td>2 HIV infection (by gender)</td>
<td>2</td>
<td>4354</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.31 [0.19, 0.50]</td>
</tr>
<tr>
<td>2.1 Women</td>
<td>2</td>
<td>1729</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.40 [0.23, 0.71]</td>
</tr>
<tr>
<td>2.2 Men</td>
<td>2</td>
<td>2625</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.17 [0.07, 0.41]</td>
</tr>
<tr>
<td>3 Serious adverse events</td>
<td>3</td>
<td>6862</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.00 [0.83, 1.19]</td>
</tr>
</tbody>
</table>

### Comparison 2. TDF vs placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HIV infection</td>
<td>2</td>
<td>4027</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.33 [0.20, 0.55]</td>
</tr>
<tr>
<td>2 Serious adverse events</td>
<td>1</td>
<td>3168</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.03 [0.79, 1.33]</td>
</tr>
</tbody>
</table>

### Comparison 3. TDF-FTC vs TDF alone

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HIV infection</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 Serious adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison of TDF+ FTC vs placebo, Outcome 1 HIV infection (by risk group).

Review: Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

Comparison: 1 TDF+ FTC vs placebo

Outcome: 1 HIV infection (by risk group)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TDF-FTC</th>
<th>placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baeten 2012</td>
<td>13/1579</td>
<td>52/1584</td>
<td>23.9%</td>
<td>0.25</td>
<td>[0.14, 0.46]</td>
</tr>
<tr>
<td>Thigpen 2012</td>
<td>9/601</td>
<td>24/599</td>
<td>20.6%</td>
<td>0.37</td>
<td>[0.18, 0.80]</td>
</tr>
<tr>
<td>Van Damme 2012</td>
<td>33/1024</td>
<td>35/1032</td>
<td>27.0%</td>
<td>0.95</td>
<td>[0.60, 1.52]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>3204</td>
<td>3215</td>
<td>71.5%</td>
<td>0.46</td>
<td>[0.19, 1.10]</td>
</tr>
<tr>
<td>Total events: 55 (TDF-FTC), 111 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: $\tau^2 = 0.51$; $\chi^2 = 12.85$, df = 2 ($P = 0.002$); $I^2 = 84\%$
| Test for overall effect: $Z = 1.75$ ($P = 0.081$) |
| MSM group         |         |         |            |        |            |
| Grant 2010        | 36/1251 | 64/1248 | 28.5%      | 0.56   | [0.38, 0.84] |
| **Subtotal (95% CI)** | 1251   | 1248   | 28.5%      | 0.56   | [0.38, 0.84] |
| Total events: 36 (TDF-FTC), 64 (placebo) |
| Heterogeneity: not applicable |
| Test for overall effect: $Z = 2.83$ ($P = 0.0047$) |
| **Total (95% CI)** | 4455   | 4463   | 100.0%     | 0.49   | [0.28, 0.85] |
| Total events: 91 (TDF-FTC), 175 (placebo) |
| Heterogeneity: $\tau^2 = 0.24$; $\chi^2 = 12.85$, df = 3 ($P = 0.005$); $I^2 = 77\%$
| Test for overall effect: $Z = 2.52$ ($P = 0.012$) |
| Test for subgroup differences: $\chi^2 = 0.18$, df = 1 ($P = 0.68$); $I^2 = 0.0\%$

0.05 0.2 1 5 20

Favours TDF-FTC  Favours placebo

Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

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Analysis 1.2. Comparison 1 TDF+ FTC vs placebo, Outcome 2 HIV infection (by gender).

Review: Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

Comparison: 1 TDF+ FTC vs placebo

Outcome: 2 HIV infection (by gender)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>H:Random,95% CI</td>
<td></td>
<td>H:Random,95% CI</td>
</tr>
<tr>
<td>1 Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baeten 2012</td>
<td>9/566</td>
<td>28/619</td>
<td>40.7 %</td>
<td>0.35</td>
<td>0.17, 0.74</td>
</tr>
<tr>
<td>Thigpen 2012</td>
<td>7/274</td>
<td>14/270</td>
<td>28.6 %</td>
<td>0.49</td>
<td>0.20, 1.20</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>840</strong></td>
<td><strong>889</strong></td>
<td></td>
<td><strong>69.3 %</strong></td>
<td><strong>0.40 [ 0.23, 0.71 ]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baeten 2012</td>
<td>4/1010</td>
<td>24/959</td>
<td>20.6 %</td>
<td>0.16</td>
<td>0.06, 0.45</td>
</tr>
<tr>
<td>Thigpen 2012</td>
<td>2/327</td>
<td>10/329</td>
<td>10.1 %</td>
<td>0.20</td>
<td>0.04, 0.91</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1337</strong></td>
<td><strong>1288</strong></td>
<td></td>
<td><strong>30.7 %</strong></td>
<td><strong>0.17 [ 0.07, 0.41 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 16 (Experimental), 42 (placebo)
Heterogeneity: Tau^2 = 0.0, Chi^2 = 3.33, df = 1 (P = 0.077); I^2 = 0%
Test for overall effect: Z = 3.12 (P = 0.0018)

Total events: 6 (Experimental), 34 (placebo)
Heterogeneity: Tau^2 = 0.0, Chi^2 = 0.07, df = 1 (P = 0.80); I^2 = 0%
Test for overall effect: Z = 4.00 (P = 0.000063)

**Total (95% CI)**

Total events: 22 (Experimental), 76 (placebo)
Heterogeneity: Tau^2 = 0.1; Chi^2 = 3.07, df = 3 (P = 0.38); I^2 = 2%
Test for overall effect: Z = 4.74 (P < 0.00001)
Test for subgroup differences: Chi^2 = 2.63, df = 1 (P = 0.10); I^2 = 62%
### Analysis 1.3. Comparison 1 TDF+ FTC vs placebo, Outcome 3 Serious adverse events.

Review: Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

Comparison: 1 TDF+ FTC vs placebo

Outcome: 3 Serious adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TDF-FTC</th>
<th>placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-L, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baeten 2012</td>
<td>107/1579</td>
<td>105/1584</td>
<td>47.7 % 1.02 [0.79, 1.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grant 2010</td>
<td>60/1251</td>
<td>67/1248</td>
<td>28.0 % 0.89 [0.64, 1.25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigpen 2012</td>
<td>55/601</td>
<td>51/599</td>
<td>24.4 % 1.07 [0.75, 1.55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>3431</strong></td>
<td><strong>3431</strong></td>
<td><strong>100.0 % 1.00 [0.83, 1.19]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 222 (TDF-FTC), 223 (placebo)
Heterogeneity: Tau² = 0.0, Chi² = 0.60, df = 2 (P = 0.74); I² = 0.0%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable

---

### Analysis 2.1. Comparison 2 TDF vs placebo, Outcome 1 HIV infection.

Review: Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

Comparison: 2 TDF vs placebo

Outcome: 1 HIV infection

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TDF</th>
<th>placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-L, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baeten 2012</td>
<td>17/1584</td>
<td>52/1584</td>
<td>89.6 % 0.33 [0.19, 0.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peterson 2007</td>
<td>2/427</td>
<td>6/432</td>
<td>10.4 % 0.34 [0.07, 1.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2011</strong></td>
<td><strong>2016</strong></td>
<td><strong>100.0 % 0.33 [0.20, 0.55]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 19 (TDF), 58 (placebo)
Heterogeneity: Tau² = 0.0, Chi² = 0.00, df = 1 (P = 0.97); I² = 0.0%
Test for overall effect: Z = 4.25 (P = 0.000021)
Test for subgroup differences: Not applicable

---

Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review) 41
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### Analysis 2.2. Comparison 2 TDF vs placebo, Outcome 2 Serious adverse events.

**Review:** Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

**Comparison:** 2 TDF vs placebo

**Outcome:** 2 Serious adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TDF</th>
<th>placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random</td>
<td>95% CI</td>
<td>M-H,Random</td>
</tr>
<tr>
<td>Baeten 2012</td>
<td>108/1584</td>
<td>105/1584</td>
<td>1.03</td>
<td>0.79, 1.33</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1584</strong></td>
<td><strong>1584</strong></td>
<td>1.03</td>
<td>0.79, 1.33</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 108 (TDF), 105 (placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable

### Analysis 3.1. Comparison 3 TDF-FTC vs TDF alone, Outcome 1 HIV infection.

**Review:** Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

**Comparison:** 3 TDF-FTC vs TDF alone

**Outcome:** 1 HIV infection

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TDF-FTC</th>
<th>TDF</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random</td>
<td>95% CI</td>
</tr>
<tr>
<td>Baeten 2012</td>
<td>13/1579</td>
<td>18/1584</td>
<td>0.72</td>
<td>0.36, 1.47</td>
</tr>
</tbody>
</table>

0.01 0.1 1 10 100

Favours TDF-FTC Favours TDF
Analysis 3.2. Comparison 3 TDF-FTC vs TDF alone, Outcome 2 Serious adverse events.

Review: Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

Comparison: 3 TDF-FTC vs TDF alone

Outcome: 2 Serious adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TDF-FTC</th>
<th>TDF</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Baeten 2012</td>
<td>107/1579</td>
<td>108/1584</td>
<td>0.99 [0.77, 1.29]</td>
<td>0.99 [0.77, 1.29]</td>
</tr>
</tbody>
</table>

ADDITIONAL TABLES

Table 1. Search Strategy: PubMed

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<thead>
<tr>
<th>Search</th>
<th>Most Recent Queries</th>
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<tbody>
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<td>#7</td>
<td>Search #6 NOT pregnan*</td>
</tr>
<tr>
<td>#6</td>
<td>Search #1 AND #2 AND #5</td>
</tr>
<tr>
<td>#5</td>
<td>Search #3 OR #4</td>
</tr>
<tr>
<td>#4</td>
<td>Search tenofovir OR TNF OR TDF OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil</td>
</tr>
</tbody>
</table>
### Table 1. Search Strategy: PubMed (Continued)

<table>
<thead>
<tr>
<th>ID</th>
<th>Search</th>
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</table>

### Table 2. Search strategy: Cochrane Central register

<table>
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<tr>
<th>ID</th>
<th>Search</th>
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</thead>
<tbody>
<tr>
<td>#1</td>
<td>MeSH descriptor HIV Infections explode all trees</td>
</tr>
<tr>
<td>#2</td>
<td>MeSH descriptor HIV explode all trees</td>
</tr>
<tr>
<td>#3</td>
<td>hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNODEFICIENCY SYNDROME</td>
</tr>
<tr>
<td>#4</td>
<td>MeSH descriptor Lymphoma, AIDS-Related, this term only</td>
</tr>
<tr>
<td>#5</td>
<td>MeSH descriptor Sexually Transmitted Diseases, Viral, this term only</td>
</tr>
<tr>
<td>#6</td>
<td>(#1 OR #2 OR #3 OR #4 OR #5)</td>
</tr>
<tr>
<td>#7</td>
<td>MeSH descriptor Chemoprevention explode all trees</td>
</tr>
<tr>
<td>#8</td>
<td>pre-exposure prophylaxis:ti,ab,kw OR preexposure prophylaxis:ti,ab,w OR PREP:ti,ab,kw OR anti-retroviral chemoprophylaxis:ti,ab,kw OR pan retroviral chemoprophylaxis:ti,ab,kw OR hiv prophylaxis:ti,ab,kw</td>
</tr>
<tr>
<td>#9</td>
<td>(#7 OR #8)</td>
</tr>
<tr>
<td>#10</td>
<td>tenofovir OR TNF OR TDF OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil</td>
</tr>
<tr>
<td>#11</td>
<td>(#9 OR #10)</td>
</tr>
<tr>
<td>#12</td>
<td>(#6 AND #11)</td>
</tr>
</tbody>
</table>
Table 3. EMBASE Search strategy

<table>
<thead>
<tr>
<th>No.</th>
<th>Query</th>
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</thead>
<tbody>
<tr>
<td>#8</td>
<td>#6 NOT pregnan*</td>
</tr>
<tr>
<td>#7</td>
<td>#6 NOT pregnan*</td>
</tr>
<tr>
<td>#6</td>
<td>#1 AND #2 AND #5</td>
</tr>
<tr>
<td>#5</td>
<td>#3 OR #4</td>
</tr>
<tr>
<td>#4</td>
<td>'tenofovir'/syn OR tnf OR tdf OR 'pmpa'/syn OR 'viread'/syn OR 'emtricitabine'/syn OR emc OR 'truvada'/syn OR 'emtriva'/syn OR 'coviracil'/syn</td>
</tr>
<tr>
<td>#3</td>
<td>'pre-exposure prophylaxis' OR 'preexposure prophylaxis' OR prep OR 'anti-retroviral chemoprophylaxis' OR 'antiretroviral chemoprophylaxis' OR 'chemoprevention'/syn OR 'hiv prophylaxis' OR 'chemoprophylaxis'/syn</td>
</tr>
<tr>
<td>#2</td>
<td>random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/de OR 'crossover procedure'/de OR 'double-blind procedure'/de OR 'single-blind procedure'/de OR 'randomised controlled trial'/de OR 'randomised controlled trial' OR allocat*:ti OR allocat*:ab</td>
</tr>
<tr>
<td>#1</td>
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**Feedback**

Feedback on risk of bias assessment, 22 October 2012

**Summary**

Name: Kenneth F. Schulz, PhD, MBA; Lut Van Damme, MD, PhD; Douglas J. Taylor, PhD Email Address: KSchulz@FHI360.org
Affiliation: FHI 360
Role: Distinguished Scientist; Senior Scientist; Senior Scientist
Comment: In this review of "Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals," we disagree with the review authors’ risk of bias judgment on one item for the Van Damme 2011 trial. Please note, the trial report has now been published in the New England Journal of Medicine. As for our background, Dr. Schulz is a coauthor of The Cochrane Collaboration’s tool for assessing risk of bias in randomized trials, and Dr. Taylor is the lead statistican of Van Damme 2011.

Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

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In figure 3 of the Cochrane Review, the review authors judged the Van Damme 2011 trial to be at “High risk of bias” in the “Other bias” category presumably because it “…was stopped early after an interim analysis showed that the trial was unlikely to demonstrate a protective effect of oral TDF-FTC.” We do not understand how such a judgment could ever be made on a well-designed and well-conducted randomized trial simply because it was stopped early by a data monitoring committee, even before the recent update to the Cochrane Handbook in 2011. However, that update squelched any doubt. The 2011 version clearly states under “Reconsideration of eligible issues for ‘other bias’, including early stopping of a trial” that “The guidance for the ‘other bias’ domain has been edited to strengthen the guidance that additional items should be used only exceptionally, and that these items should relate to issues that may lead directly to bias. In particular, the mention of early stopping of a trial has been removed, because (i) simulation evidence suggests that inclusion of stopped early trials in meta-analyses will not lead to substantial bias, and (ii) exclusion of stopped early trials has the potential to bias meta-analyses towards the null (as well as leading to loss of precision).” Clearly, we believe the Van Damme 2011 trial should not be judged as “high risk of bias” on this item. We suggest the reviewers correct this oversight and update the review.

The review authors also noted that only two studies were terminated early, Peterson 2007 and Van Damme 2011. However, at least two other trials in their review terminated early, in whole or in part, and the authors did not note those terminations. In Thigpen 2011, the investigators decided to proceed to orderly closure based on low retention. In Baeten 2011, the investigators changed its design after the July 2011 meeting of their DSMB because their board recommended that the results of the study be publicly reported and the placebo treatment discontinued, because predetermined stopping rules were met with the demonstration of HIV-1 protection from PrEP. These results were published in the same 2012 issue of the New England Journal of Medicine as the Van Damme 2011 trial.

Kenneth F. Schulz, PhD, MBA; Distinguished Scientist, FHI 360
Lut Van Damme, MD, PhD; Senior Scientist, FHI 360
Douglas J. Taylor, PhD; Senior Scientist, FHI 360

References

I have modified the conflict of interest statement below to declare my interests:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback, except that all three of the authors of this comment are employed by FHI 360, the organization that conducted and published the research paper discussed in this Comment.

Reply
Dear Dr. Schulz, Dr. Van Damme and Dr. Taylor,
Thank you very much for bringing this to our attention. We used the Cochrane tool for assessing risk of bias (in the current version of the printed Cochrane Handbook) which mentions early stoppage of trials as other sources of bias (Cochrane Handbook Chapter 8, page 201). However, you are correct that there is a revised version of Chapter 8 in the online version of the Handbook, and that the mention of early stopping of a trial has been removed. We agree with your comments and have made the necessary changes in the risk of bias assessment. Thank you.
Charles Okwundu

Contributors
Charles I. Okwundu, Olalekan Uthman
WHAT'S NEW
Last assessed as up-to-date: 17 October 2012.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tr>
<td>9 November 2012</td>
<td>Feedback has been incorporated</td>
<td>Added feedback, and response to feedback.</td>
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HISTORY
Review first published: Issue 1, 2009

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<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tr>
<td>15 June 2012</td>
<td>New citation required and conclusions have changed</td>
<td>New citation; conclusions changed.</td>
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<tr>
<td>15 June 2012</td>
<td>New search has been performed</td>
<td>New searches; review completely updated.</td>
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CONTRIBUTIONS OF AUTHORS
Charles Okwundu conceptualised the protocol.
Charles Okwundu and Olalekan Uthman reviewed search outputs, selected studies for inclusion, located copies of study reports, and extracted data.
Charles Okwundu wrote the review. Olalekan Uthman and Christy Okoromah provided input into the draft review.

DECLARATIONS OF INTEREST
None known

SOURCES OF SUPPORT
Internal sources

- Centre for Evidence-Based Health Care, Stellenbosch University, South Africa.

External sources

- Review for Africa Programme, South Africa.
  Charles I. Okwundu and Olalekan Uthman were awarded a Reviews for Africa Programme Fellowship (www.mrc.ac.za/cochrane/rap.htm), funded by a grant from the Nuffield Commonwealth Programme, through the Nuffield Foundation
  - The Nuffield Commonwealth Foundation, UK.
  - The South African Cochrane Center, South Africa.

Differences between protocol and review

The following aspects of the review were not in the protocol: abstract, plain language summary, risk of bias table, results, characteristics of included studies, search strategies, discussion, and authors' conclusion.

Index terms

Medical Subject Headings (MeSH)

*Premedication; Adenine [administration & dosage; *analogs & derivatives; therapeutic use]; Administration, Oral; Anti-HIV Agents [administration & dosage; *therapeutic use]; Deoxycytidine [administration & dosage; *analogs & derivatives; therapeutic use]; Drug Therapy, Combination [methods]; HIV Infections [*prevention & control]; Organophosphonates [administration & dosage; *therapeutic use]; Randomized Controlled Trials as Topic; Risk; Risk-Taking; Unsafe Sex

MeSH check words

Female; Humans; Male