

GUIDANCE ON PRE-EXPOSURE ORAL PROPHYLAXIS (PrEP)  
FOR SERODISCORDANT COUPLES, MEN AND TRANSGENDER  
WOMEN WHO HAVE SEX WITH MEN AT HIGH RISK OF HIV:  
Recommendations for use in the context of demonstration projects

July 2012





**GUIDANCE ON PRE-EXPOSURE ORAL PROPHYLAXIS (PrEP)  
FOR SERODISCORDANT COUPLES, MEN AND TRANSGENDER  
WOMEN WHO HAVE SEX WITH MEN AT HIGH RISK OF HIV:**  
Recommendations for use in the context of demonstration projects

July 2012

#### WHO Library Cataloguing-in-Publication Data

Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects.

1.HIV infections. 2.Anti-HIV agents - therapeutic use. 3.HIV seronegativity. 4.HIV seropositivity - transmission. 5.Transsexualism. 6.Homosexuality, Male. I.World Health Organization.

ISBN 978 92 4 150388 4

(NLM classification: WC 503.6)

© World Health Organization 2012

All rights reserved. Publications of the World Health Organization are available on the WHO web site ([www.who.int](http://www.who.int)) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: [bookorders@who.int](mailto:bookorders@who.int)).

Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press through the WHO web site ([http://www.who.int/about/licensing/copyright\\_form/en/index.html](http://www.who.int/about/licensing/copyright_form/en/index.html)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

Printed in the United States of America.

# 1. BACKGROUND

Globally, 34 million people are living with HIV. A number of HIV prevention methods are available, including male and female condoms, voluntary medical male circumcision, prevention of mother-to-child HIV transmission (PMTCT) and harm reduction strategies such as provision of sterile injecting equipment and opiate substitution therapy for people who inject drugs. All these have contributed to a levelling of the rate of new infections in some countries. Elsewhere, however, the momentum of the epidemic remains strong. In 2010 alone an estimated 2.7 million people became newly infected with HIV. Additional safe and effective approaches to HIV prevention are urgently needed.

The field of HIV prevention, until recently, experienced years of disappointment, as the search for potential vaccines and non-antiretroviral microbicides has yielded little result. Now, however, a promising new approach has emerged: the use of antiretroviral drugs for HIV prevention, both for those uninfected and for those already living with HIV (1–3).

These recommendations have been developed specifically to address the daily use of antiretrovirals in HIV-uninfected people to block the acquisition of HIV infection. This prevention approach is known as pre-exposure prophylaxis (PrEP). At this stage evidence is available from studies with two groups: men and transgender women<sup>1</sup> who have sex with men; and serodiscordant heterosexual couples. In parallel, the World Health Organization (WHO) also is preparing new recommendations on the use of antiretroviral drugs in people living with HIV to prevent transmission of infection.

## 1.1 Why is guidance needed?

Clinical trials of daily oral PrEP for uninfected individuals have shown evidence of effectiveness (4–6). These clinical trials have focused on two regimens, (i) a daily fixed-dose combination of 300 mg tenofovir disoproxil fumarate (TDF) and 200 mg emtricitabine (FTC) and (ii) 300 mg of TDF alone. The safety of these regimens has been established in these effectiveness trials (4–6), through their use as therapeutic agents in the treatment of AIDS and in a safety trial in uninfected people (7). Trials of additional drugs for PrEP and different modes of administration are now starting.

Although the evidence of effectiveness is strong, it remains unclear how PrEP may best be implemented and scaled up in settings where its use might be most beneficial. While the effects on risk behaviours, values, preferences and resource costs have been studied in conjunction with the clinical trials, they are not well understood in actual application, and so the feasibility of PrEP implementation is not known. Therefore, experience with using PrEP outside the context of controlled clinical trials is needed. For this, WHO is encouraging countries to

---

<sup>1</sup> Transgender women are birth-assigned males who identify and/or present as female, or as members of another broadly feminized gender (in cultures in which it is accepted that more than two genders may exist).

undertake demonstration projects and will offer advice on key questions and areas that could be addressed to facilitate understanding of the safety, effectiveness and sustainability of daily oral PrEP and its use as an addition to existing HIV prevention efforts (see Section 4, Need for demonstration projects). The outcome of these demonstration projects and country experience will also be used by WHO in three to five years' time to develop guidance for the implementation and scale-up of PrEP.

## 2. OVERVIEW OF PREP RESEARCH

Clinical trials on PrEP began in 2005. These trials have focused on the effectiveness of PrEP among people who inject drugs, HIV serodiscordant couples, heterosexual men and women, women at higher risk of HIV exposure, and men and transgender women who have sex with men (MSM-TG). Of these, two have completed as planned, one was stopped early for effectiveness, and two others were stopped or had arms discontinued for reasons of futility. The next section provides an overview of these trials. Section 3, Recommendations and the annexes (published on the Internet at [http://www.who.int/hiv/pub/arv/prev\\_annex/en/](http://www.who.int/hiv/pub/arv/prev_annex/en/)) provide more detail about the clinical trials addressing the two populations that are the focus of this guidance.

### 2.1 Clinical trials

The first daily oral PrEP trial to produce results was the 6-country iPrEx trial (4). This trial tested the combination of TDF and FTC in men who have sex with men and transgender women who have sex with men. It is the only Phase III trial of daily oral PrEP among MSM that has been completed, and no other trials are currently under way. iPrEx is included in the systematic review for the second PICO<sup>1</sup> question (see Section 2.2, Systematic review of evidence). This trial found an overall reduction in HIV acquisition of 44%, with higher effectiveness in the most adherent users. In participants with measurable drug levels at clinic visits (indicating better adherence), effectiveness in preventing HIV acquisition reached 90%.

The second trial of daily oral TDF/FTC involved African women at higher risk of HIV in Kenya, South Africa and the United Republic of Tanzania. This trial was terminated early due to futility, that is, the inability to reach a conclusion: an equal number of infections were seen in the PrEP and placebo arms at interim analysis. The likely cause is poor adherence, with resultant low drug concentrations in study participants. Definitive conclusions are not yet available, however (8).

The third trial, the TDF2 study conducted in Botswana, studied daily use of oral TDF/FTC among heterosexual men and women (6). In this Phase IIb trial, PrEP reduced the risk of acquiring HIV infection by roughly 63% overall.

The fourth trial, Partners PrEP, evaluated daily oral TDF alone and daily oral TDF/FTC among HIV-1 serodiscordant couples in Kenya and Uganda. This study is included in the systematic review for the first PICO question. This trial found an overall effectiveness of 67% with TDF alone and 75% with TDF/FTC (5). With higher levels of adherence (as suggested by TDF levels in plasma), the effectiveness of oral TDF was 86% and of the TDF/FTC combination was 90% (9).

---

<sup>1</sup> PICO is an acronym that describes the elements of a well-formed clinical question. The structure includes: "P" for the patient or population; "I" for the intervention of interest; "C" for comparison; and "O" for outcome.

Two intervention arms of a fifth trial were stopped for futility. The VOICE trial, a trial being conducted among women in Uganda, South Africa and Zimbabwe, was assessing the effectiveness of daily oral TDF, daily oral TDF/FTC, and daily topical TDF gel, all compared with placebos. The daily oral TDF and the daily TDF gel arms were stopped when interim analysis found that a conclusion on the effectiveness of these two interventions could not be reached in this trial. The study will continue with daily oral TDF/FTC and is expected to produce results in early 2013.

Few concerns about safety, resistance or increased risky behaviour arose in any of the completed trials, which have involved more than 8000 participants.

In addition to these trials, one trial of tenofovir gel also has completed (10). This product, used as a vaginal gel inserted both before and after intercourse, reduced acquisition of HIV infection in women by 39% overall, again with higher effectiveness among the more adherent users.

## 2.2 Systematic review of evidence

The development of this guidance consisted of systematic reviews of effectiveness and safety, GRADE<sup>1</sup> profile analysis, reviews of values and preferences of potential users and consultations with key scientists, implementers and peer reviewers. Three groups were formed to analyse the evidence and review this guidance: the Guidelines Steering Group consisting of WHO experts, the full Guidelines Development Group, and the External Review Group. The members and declarations of conflicts of interests are listed in the annexes.

The two systematic reviews examined evidence for the following PICO questions:

1. Should daily tenofovir (TDF) or daily tenofovir (TDF) plus emtricitabine (FTC) be used as pre-exposure prophylaxis for HIV prevention for the uninfected partner in heterosexual HIV-serodiscordant couples?
2. Should daily oral tenofovir (TDF) and emtricitabine (FTC) be used as pre-exposure prophylaxis for HIV prevention among men and transgender women who have sex with men?

The systematic reviews for both questions found limited but high-quality evidence of the effectiveness of oral PrEP, with evidence of acceptability for the intended populations. For the use of PrEP in serodiscordant couples, the systematic review found one randomized controlled trial (RCT) directly addressing this population. For the use of PrEP in men who have sex with

---

<sup>1</sup> GRADE is an acronym for the Grading of Recommendations Assessment, Development and Evaluation (11,12).



men and transgender women, a systematic review again found one RCT directly addressing this population. No observational studies were found. The results of the systematic reviews were ranked using the GRADE method (11,12). Both studies were assessed as high-quality evidence. Complete details of the systematic reviews are available online at [http://www.who.int/hiv/pub/arv/prep\\_annex/en/](http://www.who.int/hiv/pub/arv/prep_annex/en/). In section 3, the application of the evidence to the development of the recommendations is described after each recommendation.

## 3. RECOMMENDATIONS

### 3.1 Use of PrEP by serodiscordant couples<sup>1</sup>

In serodiscordant couples efforts to prevent HIV/STI should first and foremost follow the recommendations set forth in *Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples* (13). This guidance recommends the use of early treatment with antiretrovirals for the infected partner to reduce chances of HIV transmission. Countries should decide what to recommend to serodiscordant couples: early initiation of treatment for the infected partner, PrEP for the uninfected partner, or a combination of the two. Best approaches will likely vary across contexts and may need to be tailored to specific situations.

#### **Recommendation 1:**

In countries where HIV transmission occurs among serodiscordant couples, where discordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner.

*Conditional recommendation, high quality of evidence*

It is currently not possible to develop definitive guidance on how best to deliver daily oral PrEP to the HIV-uninfected partners (male or female) in serodiscordant couples; demonstration project research is needed (see Section 4).

If PrEP is to be provided for same-sex serodiscordant couples, the combination of FTC and TDF should be used, as the evidence of effectiveness and safety in male-to-male penetrative sexual behaviour is available for only this regimen.

#### **Evaluating and grading the evidence for serodiscordant couples**

The quality of the evidence was judged to be high, as one multi-country RCT without serious limitations directly addressed this population. The Partners PrEP study found that both formulations of oral PrEP were associated with reduced risk of HIV-1 infection compared with placebo (5). This reduction was 67% for TDF (hazard ratio (HR): 0.33, 95% CI 0.19–0.56,  $p < 0.001$ ) and 75% for TDF/FTC (HR: 0.25, 95% CI 0.13–0.45,  $p < 0.001$ ). These effects were not statistically different by sex. No significant difference was reported in adverse events between either the TDF or the TDF/FTC arm and the control arm. All groups reported reduced frequency of sex without condoms over the course of the intervention, but no significant differences in condom use rates or in rates of reported outside sexual partners were observed between the TDF, TDF/FTC and control arms.

<sup>1</sup> In this guidance couples are defined as two persons in an on-going sexual relationship, and no distinction is made between heterosexual and same-sex couples.

A review of the literature on values and preferences found only one study that directly addressed serodiscordant couples (14), although others had studied heterosexual and homosexual adults. The existing literature indicates general acceptability of oral PrEP overall, including among serodiscordant couples (Annex 3).

Resources required for PrEP use were judged to be possibly an important consideration in the decision to implement this intervention in certain settings. This point has been addressed in mathematical modelling (15). In the model, although the cost of PrEP was high, the cost per infection averted was significantly offset by future savings in lifelong treatment, especially among couples with multiple partners, low rates of condom use and a high risk of transmission. In some situations PrEP could be cost-saving overall. Using sexual risk behaviour data from the Partners in Prevention trial (16), the cost per HIV infection averted was between US\$6000 and \$66 000 when PrEP was always used, and the savings per quality-adjusted life year (QALY), a standard measure of cost-benefit, was \$260 to \$4900. Using “more typical” data that assume less risky sexual behaviour, the cost per HIV infection averted was between ~\$0 (break-even) and \$26 000 when PrEP was always used, and the cost per QALY gained was between minus \$200 (cost-saving) and \$1900.

Feasibility was also judged to be an important consideration in the decision to implement PrEP in certain settings. Oral PrEP for heterosexual HIV serodiscordant couples has proved feasible in various trial settings. However, adherence to daily oral medication may prove challenging over longer periods of time.

PrEP was recommended due to the positive balance of benefits and harms based on high-quality evidence, acceptability in the values and preferences review, feasibility in trial settings, and potential cost-effectiveness. However, resource use and feasibility in non-trial settings are uncertain; no data are available on long-term health effects of TDF/FTC in HIV-uninfected individuals or among those who become HIV-infected while on PrEP; and sexual risk behaviour and adherence to PrEP medications might be different outside a trial setting. For these reasons the recommendation is conditional.

### **3.2 Use of PrEP by men and transgender women who have sex with men**

In MSM-TG efforts to prevent HIV/STIs should first and foremost follow the recommendations set forth in *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people* (17).

**Recommendation 2:**

In countries where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral PrEP (specifically the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention.

*Conditional recommendation, high quality of evidence*

It is currently not possible to provide definitive guidance on how best to deliver daily oral PrEP to MSM-TG; demonstration project research is needed (see Section 4).

**Evaluating and grading the evidence for men and transgender women who have sex with men**

The quality of the evidence was judged to be high, as a multi-country RCT without serious limitations directly addressed this population. The iPrEx study (4) found that oral PrEP with TDF/FTC was associated with reduced risk of HIV in both intention-to-treat analysis (HR: 0.53, 95% CI 0.36–0.78,  $p=0.001$ ) and modified intention-to-treat analysis (HR: 0.56, 95% CI 0.37–0.85,  $p=0.005$ ). No significant difference in reported adverse events between the TDF/FTC and control arms was found. Both groups reported increased condom use over the course of the intervention, but condom use rates and reported number of sexual partners did not differ significantly between study arms.

A review of the literature on values and preferences found studies conducted among MSM-TG in several settings that generally supported the availability of PrEP (Annex 6). Studies in the United States reported increasing awareness of PrEP among MSM. Between 44% and 74% of MSM across studies said they would consider taking PrEP themselves. Positive perceptions of PrEP include user-friendliness and potential benefits of use in serodiscordant relationships. Concerns include potential side-effects, potential sexual risk disinhibition, stigma and discrimination associated with PrEP use, and mistrust of health-care professionals. Factors affecting PrEP acceptability included efficacy (most studies were conducted before the release of the iPrEx trial results), potential side-effects and out-of-pocket costs.

Resources required for PrEP use were judged as possibly an important consideration in the decision to implement this intervention in certain settings. One cost-effectiveness study in Australia estimated that, if continuous use of PrEP was 90% effective and the program covered only HIV-negative MSM having high-risk sex, it would cost US\$47 745 per QALY gained (18). Another cost-effectiveness study from the USA estimated that if PrEP was 90% effective and the program covered only HIV-negative MSM having high-risk sex, it would cost US\$107 000 per QALY gained (19). If PrEP was 50% effective, it would cost US\$298 000 per QALY gained. Sensitivity analyses showed that the cheaper and more efficacious PrEP

is and the more high-risk the population is, the more cost-effective that PrEP would be, with estimates in cost-*saving* ranging up to over US\$300 000 per QALY gained (20). Overall, cost-effectiveness estimates vary widely, depending on model parameter estimates, including efficacy, cost of PrEP, HIV incidence and age of the population.

Feasibility was also judged to be an important consideration in the decision to implement PrEP in certain settings. Oral PrEP for MSM has proved feasible in trial settings. However, adherence to daily oral medication may prove challenging over longer periods of time. Issues of criminalization, stigma and discrimination, and violence should be considered during implementation, especially where MSM-TG behaviour is illegal.

PrEP was recommended due to the positive balance of benefits and harms based on high-quality evidence, acceptability in the values and preferences review, feasibility in trial settings, and potential cost-effectiveness. However, resource use and feasibility in non-trial settings are uncertain; no data exist on long-term health effects of TDF/FTC in HIV-uninfected individuals or among those who become HIV-infected while on PrEP; sexual risk behaviour and adherence to PrEP medications might be different outside of a trial setting; and concerns may exist about criminalization, stigma, discrimination, and violence when implementing PrEP for MSM-TG in certain settings. For these reasons the recommendation was conditional.

### **3.3 Use of PrEP by other groups**

The Guidelines Development Group that formulated these recommendations has not reviewed the evidence on the preventive effect of PrEP in groups other than those described in the PICO questions and the systematic reviews. However, international scientific consensus is emerging that antiretroviral drugs, including PrEP, significantly reduce the risk of sexual acquisition and transmission of HIV regardless of population or setting. This consensus is supported, in the case of PrEP, by additional evidence from the TDF2 trial conducted in Botswana among sexually active heterosexual men and women (6).

## 4. NEED FOR DEMONSTRATION PROJECTS

Countries that decide to proceed with introducing oral PrEP should undertake demonstration projects to ascertain the most appropriate groups and the best delivery approaches, being attentive to the following key points:

- **Assuring, to the greatest extent possible, HIV-negative status before initiation of PrEP**

In the completed trials the development of resistant virus, which was rare, was seen only in those who tested false negative and were then placed on PrEP. Symptoms of acute nonspecific viral infections were seen in some cases, but no clear evidence of HIV by antibody testing was found. Assuring that those seeking PrEP are truly uninfected is an important step to minimize the development of resistance among those who become infected while taking antiretrovirals for PrEP.

- **Assessing the likelihood that PrEP is an appropriate strategy for an individual as an addition to other prevention measures such as condom use and STI treatment**

All PrEP trials achieved results through combination prevention, with strong emphasis on increased and continued condom use. Providing PrEP while avoiding the displacement of existing condom use is crucially important.

- **Assessing clinical contraindications such as pre-existing renal or bone disease and monitoring safety among oral PrEP users, specifically screening for adverse events**

Although well-tolerated by users in the clinical trials, TDF/FTC can cause some adverse events—specifically, modest decreases in bone mineral density and renal functioning. Evidence of serious adverse events was not found in the completed clinical trials. Nonetheless, the use of these drugs in uninfected people requires special caution. Countries may wish to track the safety of PrEP in long-term users.

- **Fostering and supporting high levels of adherence among PrEP users**

PrEP effectiveness is strongly correlated with daily adherence. Delivering PrEP in a way that fosters high levels of adherence, and that regularly assesses adherence, will be essential to implementing an effective PrEP intervention.

- **Identifying most suitable points for oral PrEP delivery and resupply**

People using PrEP will need easy access to an uninterrupted supply of the drugs. They will also have to be assessed periodically for any safety concerns, possible breakthrough HIV infections, adherence and continued risk reduction practices including condom use. Balancing the conditions needed to assure safe and effective delivery of PrEP with convenience for the user of PrEP will require creative approaches.

- **Periodic HIV retesting of oral PrEP users to detect any breakthrough infections in a timely manner**

While PrEP can be effective when used as indicated, HIV infections can still occur. Retesting is important for the prompt detection of new infections. The best interval for periodic retesting is not yet clear and could be highly specific to context. The completed PrEP trials have provided helpful evidence that the risk of drug resistance from PrEP use during acute HIV infection is slight. Estimated HIV incidence in a population, rates of change in sexual partners and condom use all should be taken into account when setting an interval for retesting.

- **Developing bridging procedures for testing those who become infected while taking PrEP, including assessing emtricitabine (FTC) and tenofovir (TDF) drug resistance among those who seroconvert while on PrEP**

Countries must decide what steps to take if people taking PrEP become infected. Procedures for removing these people from PrEP, supplementing the TDF/FTC with other drugs for complete early treatment and other interim approaches must be established, in line with national AIDS treatment policy. Careful consideration needs to be given to different situations that clinicians are likely to encounter and how best to address these situations in service delivery.

- **Developing transition mechanisms for those who wish or need to stop taking PrEP**

Those who no longer can or who choose to stop PrEP will need continued access to other HIV prevention services and risk reduction.

- **Gathering additional information to facilitate decision-making about ethical issues in countries where drug supplies and resources are limited and universal access to treatment has not been achieved**

Countries will need to assess how best to allocate their available resources for HIV prevention, considering the relative cost-benefit of PrEP within combination prevention, so as to guide choices and assess the social, cultural and political feasibility of delivering PrEP.

## 5. REVIEW PROCESS

Following the publication of the iPrEx trial results in November 2010, WHO convened a small consultation in February 2011 to take external advice on whether and how WHO should proceed. The participants at that consultation, Jorge Beloqui, Peter Fajans, Timothy Farley, Robert Grant, Cate Hankins, Petchsri Sirinirund, Dawn Smith, and staff members of the WHO HIV Department, agreed that it was not possible to develop full implementation guidelines at that time. However, given the importance of the data presented in the publication of the iPrEx results and the need for implementation information, it was agreed to seek approval from the WHO Guidelines Review Committee (GRC) for the development of guidance concerning men who have sex with men and transgender women.

Application for GRC approval was made in March 2011, and the GRC reviewed the proposal in its June 2011 meeting. Work to develop the guidance began immediately thereafter. In late June 2011 evidence from two additional trials was produced: the TDF2 trial was completed, and the Partners PrEP trial was stopped early for overwhelming evidence of effectiveness. The decision was taken to seek GRC approval to expand the guidance to include serodiscordant couples, the focus of the Partners PrEP trial. Application to the GRC for this expansion was made in September 2011 and approved at the October GRC meeting. Review of evidence on serodiscordant couples began as soon as the data from the Partners PrEP trial were released to WHO, in February 2012.

Caitlin Kennedy and Virginia Tedrow Fonner of Johns Hopkins University Bloomberg School of Public Health conducted the systematic reviews of the evidence, developed the GRADE tables and undertook the reviews of values and preferences. Eli Akl of the State University of New York at Buffalo provided methodological advice and consultation on request.

The WHO Steering Group for this effort (Kevin O'Reilly, Ying-Ru Lo, Florence Koechlin, Rachel Baggaley, Marco Vitoria) compiled the review copy and drafted the background text and justification for the guidance.

The Guideline Development Group, which did its work by e-mail and met by telephone, crafted the final recommendations. Given the nature of this review process via telephone conference, it was deemed essential, to facilitate this process, for the Steering Group to craft possible text on recommendations for the Development Group's consideration. When consensus was not immediately achieved on a point or on wording, the Steering Group crafted alternative wordings and sent them by e-mail to the Guideline Development Group. When consensus was achieved on the wording, as indicated by e-mail responses, the wording was accepted and incorporated. Members of the Guidelines Development Group were Jorge Beloqui, Carlos Caceres, Peter Cherutich, Cate Hankins, Mark Dybul, Smarajit Jana, Helen Rees, Petchsri Sirinirund and Dawn Smith. (Affiliations and areas of expertise are listed in Annex 7 at [http://www.who.int/hiv/pub/arv/prep\\_annex/en/](http://www.who.int/hiv/pub/arv/prep_annex/en/))



The External Review Group then reviewed the revised consensus draft. The members of the External Review Group suggested some alternative wordings to the text, but the Group considered the specific recommendations appropriate, evidence-based and clearly worded overall. The members of this group were Pedro Chequer, Mean Chhi Vun, Adeeba Kamarulzaman, Lynn Paxton and Brian Pazvakavambwa. (Affiliations and areas of expertise are listed in Annex 7.)

The Bill and Melinda Gates Foundation provided financial support for the development of this guidance.

## **5.1 Monitoring the guidance**

The guidance will be reviewed and revised as full implementation guidelines for PrEP in 2015, taking into account the implementation experience gained in countries. Until that time the emergence of new evidence on the science of PrEP will be continually monitored. If, prior to 2015, new evidence suggests the need to revise the guidance offered here, that step will be undertaken and communicated directly to countries.

This guidance is being published in English, French and Spanish. It is being disseminated to countries and to WHO and UNAIDS country staff, who will be asked to support, as needed, the development of demonstration project research based on this advice.

## **5.2 Declarations of conflicts of interests**

All members of the Guidelines Development Group and the External Review Group were asked to complete a WHO declaration of interests form. Four people declared potential conflicts of interest. The WHO Steering Group discussed these and concluded that none of the potential conflicts of interest was significant.<sup>1</sup>

---

<sup>1</sup> One panel member, Carlos Caceres, had received travel support from the institution that conducted one of the key studies reviewed. As no personal benefit would result from his work on this guidance, this was not considered a conflict of interest. One external peer reviewer, Lynn Paxton, declared that Gilead Sciences, the maker of the drugs reviewed in this guidance, had provided drugs to her institution for a study in Botswana. As no personal benefit to Dr Paxton resulted, the Steering Group decided that no conflict of interest existed. Two others reported professional responsibilities for PrEP. The Steering Group found this was not a conflict of interest.

## REFERENCES

1. Abdool Karim SS et al. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. *The Lancet*, 2011, 378:279–281.
2. Padian NS et al. HIV prevention transformed: the new prevention research agenda. *The Lancet*, 2011, 378:269–278.
3. Cohen MS et al. Prevention of HIV-1 infection with early antiretroviral therapy. *New England Journal of Medicine*, 2011, 365(6):493–505.
4. Grant R et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine*, 2010, 363(27):2587–2599.
5. Baeten JM et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New England Journal of Medicine*. Published online ahead of press 11 July 2012. <http://www.nejm.org/doi/full/10.1056/NEJMoa1108524>.
6. Thigpen MC et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England Journal of Medicine*. Published online ahead of press 11 July 2012. <http://www.nejm.org/doi/full/10.1056/NEJMoa1110711>
7. Peterson L et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clinical Trials*, 2007, 2(5):e27.
8. Van Damme L et al. Preexposure prophylaxis for HIV infection among African women. *New England Journal of Medicine*. Published online ahead of press 11 July 2012. <http://www.nejm.org/doi/full/10.1056/NEJMoa1202614>.
9. Donnell D et al. Tenofovir disoproxil fumarate drug levels indicate PrEP use is strongly correlated with HIV-1 protective effects: Kenya and Uganda. 19th Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, 2012. Abstract 30.
10. Abdool Karim Q et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*, 2010, 329:1168–1174.
11. Guyatt GH et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, 2011, 64:383–394.
12. Guyatt GH et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *Journal of Clinical Epidemiology*, 2011, 64:407–415.
13. *Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples*. Geneva, World Health Organization, April 2012. <http://www.who.int/hiv/pub/guidelines/9789241501972/en/>
14. Brubaker SG et al. Theoretical acceptability of four interventions to reduce the risk of HIV transmission among HIV discordant couples trying to conceive. In: International AIDS Society. 6<sup>th</sup> IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy, 2011.
15. Hallett TB et al. Optimal uses of antiretrovirals for prevention in HIV-1 serodiscordant heterosexual couples in South Africa: a modelling study. *PLoS Medicine*, 8(11):e1001123. doi:10.1371/journal.pmed.1001123
16. Celum C et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *New England Journal of Medicine*, 2010, 362(5):427–439.
17. *Prevention and treatment of HIV and other sexually transmitted infections among men who sex with men and transgender people*. Geneva, World Health Organization, June 2011. [http://www.who.int/hiv/pub/guidelines/msm\\_guidelines2011/en/](http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/)
18. Anderson J, Cooper D. Cost-effectiveness of pre-exposure prophylaxis for HIV in an MSM population. *HIV Medicine*, 2009, 10:39.
19. Desai K et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. *AIDS*, 2008, 22(14):1829–1839.
20. Paltiel AD et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. *Clinical Infectious Diseases*, 2009, 48(6):806–815.

For more information, contact:

World Health Organization  
Department of HIV/AIDS  
20, avenue Appia  
1211 Geneva 27  
Switzerland

E-mail: [hiv-aids@who.int](mailto:hiv-aids@who.int)

<http://www.who.int/hiv/en/>

ISBN 978 92 4 150388 4



9 789241 503884

**Guidance on Pre-exposure oral prophylaxis (PrEP) for serodiscordant couples,  
men who have sex with men and transgender women at high risk of HIV in  
implementation research**

**Annexes**

- Annex 1 - Pre-exposure prophylaxis (PrEP) for HIV serodiscordant couples: a systematic review**
- Annex 2 - GRADE table for systematic review of serodiscordant couples**
- Annex 3 - PrEP for serodiscordant couples: values and preferences review of the literature**
- Annex 4 - Pre-exposure prophylaxis (PrEP) for men and transgender women who have sex with men (MSM and TG): a systematic review**
- Annex 5 - GRADE table for systematic review of MSM/TG**
- Annex 6 - PrEP for MSM/TG: values and preferences review of the literature**
- Annex 7 - Members of external groups**

# **Annex 1- Pre-exposure prophylaxis (PrEP) for HIV serodiscordant couples: a systematic review**

## **Background**

More than 34 million people globally are living with HIV. A number of prevention methods are available, from condoms to male circumcision, PMTCT or clean needles, but to date these have not been sufficient to stop the epidemic. In 2009 alone, an estimated 2.7 million people became newly infected. Additional safe and effective approaches to HIV prevention are urgently needed.

PrEP is the use of an antiretroviral drug to block the acquisition of HIV infection by uninfected people. Proof of concept has long been established in the laboratory by animal studies and in real world application by the prevention of mother-to-child transmission and post-exposure prophylaxis. The safety of the drugs being considered for PrEP, tenofovir and emtricitabine, has been established through their use for treatment and in safety trials in uninfected people (Peterson et al., 2007). Five trials of effectiveness of oral PrEP (Phase IIb and Phase III) have been conducted since 2005. These focus on effectiveness of PrEP among injection drug users, serodiscordant couples, heterosexual women and high risk men who have sex with men.

The first trial to produce results was the iPrex trial (Grant et al., 2010). This multi-site Phase III clinical trial tested whether a daily combination of tenofovir and emtricitabine could safely and effectively prevent HIV infection among men who have sex with men and transgendered women who have sex with men. The iPrex study demonstrated a 44% reduction in HIV transmission using a modified intention-to-treat analysis. Adherence to the recommended regimen was lower than expected, though it varied by country. For those men who reported taking the pills on 90% or more days, however, the efficacy of PrEP was 73%. Resistance was only found in two participants who had an existing acute HIV infection undetected at baseline and who were randomized to active drug. Few concerns about safety were detected. A marked trend toward risk reduction, specifically increased condom use and decreased number of partners, was reported in both arms and all sites.

The second study to produce results was a trial of daily oral emtricitabine and tenofovir among high-risk African women (FHI, 2011). This trial was terminated early due to lack of efficacy, with an equal number of infections in the PrEP and placebo arms.

The third trial to produce results, the TDF2 study conducted by the U.S. Centers for Disease Control and Prevention and the Botswana Ministry of Health, was a trial of daily oral emtricitabine and tenofovir for heterosexual men and women in Botswana (CDC, 2011). This study showed that PrEP reduced the risk of acquiring HIV infection by roughly 63 per cent overall.

The fourth trial to produce results, Partners PrEP, was a trial of daily oral tenofovir and daily oral emtricitabine and tenofovir among HIV-1 serodiscordant couples in Kenya and Uganda (Mujugira et al., 2011). This trial found that those who received tenofovir alone had an average of 62% fewer HIV infections (95% CI 34 to 78%,  $p=0.0003$ ) and those who received

emtricitabine and tenofovir had 73% fewer HIV infections (95% CI 49 to 85%,  $p < 0.0001$ ) than those who received placebo (University of Washington, 2011).

This systematic review examined evidence for the following PICO question: Should daily tenofovir (TDF) or daily tenofovir (TDF) plus emtricitabine (FTC) be used as pre-exposure prophylaxis for HIV prevention for the uninfected partner in heterosexual HIV serodiscordant couples?

## **Methods**

### ***PICO question***

#### **PICO 1:**

Should daily tenofovir (TDF) or daily tenofovir (TDF) plus emtricitabine (FTC) be used as pre-exposure prophylaxis for HIV prevention for the uninfected partner in heterosexual HIV serodiscordant couples?

**P:** Heterosexual HIV serodiscordant couples

**I:** Oral tenofovir alone or oral emtricitabine (FTC) and tenofovir (TDF) or the HIV-negative partner

**C:** Placebo

**O:** (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, (4) condom use, and 5) number of sexual partners

### ***Inclusion criteria***

To be included in the review, an article had to meet the following criteria:

- 1) Randomized controlled trial evaluating the use of oral emtricitabine (FTC) and/or tenofovir (TDF) for the HIV-negative partner to prevent HIV infection among heterosexual HIV serodiscordant couples.
- 2) Measured one or more of the following key outcomes: (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, 4) condom use, and 5) number of sexual partners.
- 3) Published in a peer-reviewed journal, or presented as an abstract at a scientific conference, between January 1, 1990 and November 1, 2011.

No restrictions were placed based on location of the intervention. No language restrictions were used on the search. Articles in languages other than English were translated where necessary.

Following the GRADE approach, when direct evidence from heterosexual HIV serodiscordant couples was not available for one or more of the key outcomes, indirect evidence from other populations (high-risk heterosexual adults, men who have sex with men, etc.) was used instead, but downgraded for indirectness. If evidence from other populations was not available, evidence from non-randomized but controlled studies was used instead, but also downgraded for directness.

### ***Search strategy***

The following electronic databases were searched using the date ranges January 1, 1990 to November 1, 2011: Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and EMBASE. Secondary reference searching was conducted on all studies included in the review. Further, selected experts in the field were contacted to identify additional articles not identified through other search methods.

Abstracts from the following conferences were searched from January 1, 1990 to November 1, 2011: International AIDS Conference (IAC), IAS Conference on HIV Pathogenesis, Treatment, and Prevention (IAS), and Conference on Retroviruses and Opportunistic Infections (CROI).

### ***Search terms***

The following terms were entered into all computer databases:

(“sero-discordant” or serodiscordant or discordant or couple) AND (“pre-exposure prophylaxis” or PrEP or emtricitabine or tenofovir or Truvada or FTC or TDF) AND (HIV OR AIDS)

### ***Screening abstracts***

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened by two members of the study staff. Full text articles were obtained for all selected abstracts and both reviewers independently assessed all full-text articles for eligibility to determine final study selection. Differences were resolved through consensus.

Articles not meeting the inclusion criteria for the review, but presenting potentially interesting background information relevant to PrEP among heterosexual HIV serodiscordant couples, including review articles, qualitative studies, cost or cost-effectiveness analyses, or descriptions of interventions without an evaluation component, were included in an annotated bibliography of additional articles.

### ***Data extraction and management***

Data were extracted independently by two reviewers using standardized data extraction forms. Differences in data extraction were resolved through consensus and referral to a senior team member from WHO when necessary. Study authors were contacted when additional information or data were needed.

The following information was gathered from each included study:

- Study identification: Author(s); type of citation; year of publication
- Study description: Study objectives; location; population characteristics; description of the intervention; study design; sample size; follow-up periods and loss to follow-up
- Outcomes: Analytic approach; outcome measures; comparison groups; effect sizes; confidence intervals; significance levels; conclusions; limitations

Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook, chapter 8.5 – Higgins & Green, 2011). This tool assesses random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data addressed (attrition bias), incomplete outcome data, and selective reporting (reporting bias). Methodological components of the studies were assessed and classified as high, low, or uncertain risk of bias.

### ***Data analysis***

Data were analyzed according to the data extraction categories and outcomes listed above. If multiple studies reported the same outcome, meta-analysis would have been conducted using random-effects models to combine odds ratios with the program Comprehensive Meta-Analysis (CMA). Data were summarized in GRADE evidence profiles, summary of finding tables, and risk/benefit tables.

### **Results**

Our initial database search yielded 82 citations and 292 conference abstracts; two additional studies were identified through other means, such as searching through the reference lists of relevant articles (Figure 1). One randomized trial was deemed eligible for inclusion in our review.

The one study that met all inclusion criteria was the Partners PrEP trial (Baeten et al., 2012). This study was a three arm, randomized controlled trial to evaluate the efficacy of oral PrEP (TDF and/or FTC/TDF) for HIV prevention among HIV serodiscordant heterosexual couples. The trial was conducted in 9 clinical sites in Kenya and Uganda.

Baseline characteristics of participants were equal across study arms (Mujugira et al., 2011). For 62% of enrolled couples, the HIV-1 seronegative partner was male. Median age was 33 years for HIV-1 susceptible and HIV-1 infected partners [IQR (28–40) and (26–39) respectively]. Most couples (98%) were married, with a median duration of partnership of 7.0 years (IQR 3.0–14.0) and recent knowledge of their serodiscordant status [median 0.4 years (IQR 0.1–2.0)]. For HIV-1 seropositive participants, the median CD4 count was 495 cells/mm<sup>3</sup> (IQR 375–662), 80% had CD4 counts  $\geq$  350 cells/mm<sup>3</sup>, and median plasma HIV-1 RNA level was 3.9 log<sub>10</sub> copies/mL (IQR 3.2–4.5).

Using the Cochrane Risk of Bias tool, the study was judged to have low risk of bias across all of the following categories: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data addressed (attrition bias), selective reporting (reporting bias), and other biases. The study was stopped early for evidence of benefit, which may overestimate treatment effects; however, as this was a multi-country study judged to have low risk of bias on all other criteria, it was not downgraded for this reason, and was considered high quality.

The study measured all five key outcomes for this review: 1) HIV infection, 2) Any adverse event, 3) Any stage 3 or 4 adverse event, 4) Condom use, and 5) Number of sexual partners.

### ***HIV infection***



Incident HIV infection was significantly reduced among participants in both the TDF and the FTC/TDF study arms as compared to the control arm using a modified intention-to-treat analysis excluding participants who had HIV RNA detected at baseline. There were 96 serconversions in total; 82 were post-randomization conversions. In the TDF arm, there were 17 incident cases of HIV infection out of 1579 participants (HIV incidence rate: 0.65 per 100 person years (py)) compared to 52 incident HIV infections out of 1578 participants in the control group (HIV incidence rate: 1.99 per 100 py), resulting in a hazard ratio of 0.33 (95% CI 0.19-0.56,  $p<0.001$ ), thus showing a 67% reduction in HIV acquisition (95% CI 44-81%,  $p<0.001$ ). In the FTC/TDF arm, there were 13 incidence cases of HIV infection out of 1576 participants (HIV incidence rate: 0.25 per 100 py), resulting in a hazard ratio (compared to placebo) of 0.25 (95% CI 0.13-0.45,  $p<0.001$ ), thus showing a 75% reduction in HIV acquisition. The HIV-1 protective effects of FTC/TDF and TDF were not significantly different.

These results were further stratified by gender. Among women, TDF efficacy was 71% ( $p=0.002$ ) and FTC/TDF was 66% ( $p=0.005$ ); among men, TDF efficacy was 63% ( $p=0.01$ ) and FTC/TDF was 84% ( $p<0.001$ ). The HIV-1 protective effects of TDF and FTC/TDF were not statistically different by sex.

#### ***Any adverse event***

There was no statistically significant difference in reported adverse events between study arms. In the TDF arm, 1350 out of 1584 patients (82.5%) reported having any adverse event compared to 1350 out of 1584 patients (85.2%) in the control group, which was not statistically significant ( $p=1.00$ ). In the FTC/TDF arm, 1362 out of 1579 patients (86.3%) reported having any adverse event, which was not statistically significant compared to the control group ( $p=0.42$ ).

#### ***Any stage 3 or 4 adverse event***

All three study arms also reported similar rates of stage 3 and 4 adverse events.

For stage 3 adverse events, in the TDF study arm, 289 out of 1584 patients (18.2%) reported having a grade 3 adverse event compared to 268 out of 1584 patients (16.9%) in the control arm, which was not statistically significant ( $p=0.35$ ). In the FTC/TDF study arm, 293 out of 1579 patients (18.6%) reported having a grade 3 adverse event, which was not statistically significant compared to the control group ( $p=0.24$ ).

For stage 4 adverse events, in the TDF study arm, 34 out of 1584 patients (2.1%) reported having a grade 4 adverse event compared to 39 out of 1584 patients (2.5%) in the control arm, which was not statistically significant ( $p=0.64$ ). In the FTC/TDF study arm, 44 out of 1579 patients (2.8%) reported having a grade 4 adverse event, which was not statistically significant compared to the control group ( $p=0.58$ ).

#### ***Condom use***

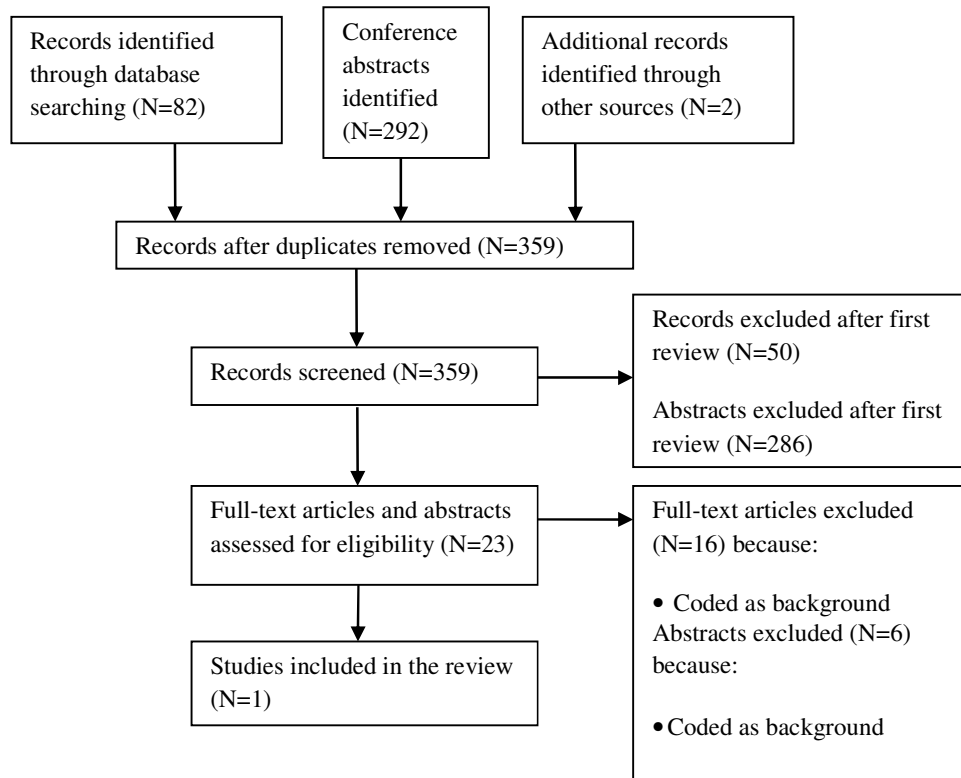
The study found that all groups reported reduced sex without condoms over the course of the intervention, but there were no significant differences in condom use rates between the TDF, FTC/TDF, and control arms. At enrollment, 27% of HIV seronegative partners reported sex

without condoms with their HIV seropositive partner during the prior month. This percentage decreased throughout the study (to 13% and 9% at 12 and 24 months) , though appeared to increase to pre-intervention levels at the end of the trial among a small number of participants who completed 36 months of follow-up. The difference across arms was not statistically significant using generalized estimating equations analysis (GEE) to assess trends over time (TDF vs. placebo:  $p=0.32$ ; FTC/TDF vs. placebo:  $p=0.66$ ).

### ***Number of sexual partners***

There was no difference in reported outside sexual partners across the three study arms. In the TDF arm, 468 out of 1584 participants (29.7%) reported an outside partner at any follow-up visit, compared with 459 out of 1584 participants (29.1%) in the control group ( $p=0.74$ ). In the FTC/TDF arm, 469 out of 1579 participants (29.9%), which was also not a statistically significant difference compared to the control group ( $p=0.67$ ).

**Figure 1: Disposition of citations during the search and screening process**



**Table 1: Risk-benefit table**

Factor	Explanation / Evidence	Judgment
<b>Quality of Evidence</b>	One multi-country RCT without serious limitations. Additional studies from other populations at various stages of completion.	<b>High</b>
<b>Balance of Benefits vs. Harms</b>	<p><b><i>HIV infection</i></b>            Oral PrEP was associated with reduced risk of HIV-1 compared to placebo. This reduction was 67% for TDF [Hazard ratio (HR): 0.33, 95% CI 0.19-0.56, p&lt;0.001] and 75% for FTC/TDF (HR: 0.25, 95% CI 0.13-0.45, p&lt;0.001). These HIV-1 protective effects of TDF and FTC/TDF were not statistically different by sex.</p> <p><b><i>Adverse events</i></b>            There was no significant difference in reported adverse events between the TDF or FTC/TDF and control arms. This was the case for any adverse event (TDF vs. control: 82.5% vs. 85.2%, p=1.00; FTC/TDF vs. control: 86.3% vs. 85.2%, p=0.42), for grade 3 adverse events (TDF vs. control: 18.2% vs. 16.9%, p=0.35; FTC/TDF vs. control: 18.6% vs. 16.9%, p=0.24), and for grade 4 adverse events (TDF vs. control: 2.1% vs. 2.5%, p=0.64; FTC/TDF vs. control: 2.8% vs. 2.5%, p=0.58).</p> <p><b><i>Condom use</i></b>            All groups reported reduced sex without condoms over the course of the intervention, but there were no significant differences in condom use rates between the TDF, FTC/TDF, and control arms. Rates across arms dropped from 27% at baseline to 13% at 12 months and 9% at 24 months.</p> <p><b><i>Number of sexual partners</i></b>            There was no difference in reported outside sexual partners across the three study arms (TDF vs. control: 29.7% vs. 29.1%, p=0.74; FTC/TDF vs. control: 29.9% vs. 29.1%, p=0.67).</p>	<b>Benefits outweigh harms</b>
<b>Values and Preferences</b>	Although few studies have examined values and preferences around PrEP for serodiscordant couples, existing research indicates acceptability.	<b>Acceptable</b>
<b>Resource Use</b>	<p>In mathematical modeling (Hallett et. al., 2011), although the cost of PrEP was high, the cost per infection averted was significantly offset by future savings in lifelong treatment, especially among couples with multiple partners, low condom use, and a high risk of transmission. In some situations, PrEP could be cost-saving overall.</p> <p>Using Partners in Prevention data:</p> <ul style="list-style-type: none"> <li>- Cost per infection averted was between US\$6,000 and \$66,000 when PrEP was always used</li> <li>- Cost per QALY saved was \$260-\$4,900</li> </ul> <p>Using “more typical” data on risk behavior</p>	<b>Consideration in certain settings</b>

	<ul style="list-style-type: none"> <li>- Cost per infection averted was between ~\$0 (break-even) and \$26,000 when PrEP was always used</li> <li>- Cost per QALY saved was -\$200 (cost-saving) to \$1,900</li> </ul> <p>Although the cost of PrEP may be high, the cost per infection averted may be offset by future savings in lifelong treatment. In some situations, PrEP could be cost-saving overall.</p>	
<b>Feasibility</b>	Oral PrEP for heterosexual HIV serodiscordant couples has proven feasible in various trial settings. Adherence to daily oral medication may prove challenging over longer periods of time.	<b>Consideration in certain settings</b>

## References for Annex 1: systematic review of serodiscordant couples

- Baeten, J. M., Donnell, D., Ndase, P., Mugo, N. R., Campbell, J. D., Wangisi, J., et al. Antiretroviral prophylaxis for HIV-1 prevention in heterosexual men and women. *New England Journal of Medicine*. In Press. CDC website. (2011). CDC trial and another major study find PrEP can reduce risk of HIV infection among heterosexuals. Available from: <http://www.cdc.gov/nchhstp/newsroom/PrEPHeterosexuals.html>. Accessed on 2 November 2011.
- FHI website. (2011). FHI to initiate orderly closure of FEM-PrEP. Available from: [http://www.fhi.org/en/AboutFHI/Media/Releases/FEM-PrEP\\_statement041811.htm](http://www.fhi.org/en/AboutFHI/Media/Releases/FEM-PrEP_statement041811.htm). Accessed on 2 November 2011.
- Grant, R. M., Lama, J. R., Anderson, P. L., McMahan, V., Liu, A. Y., Vargas, L., et al. (2010). Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *NEJM*, 363, (27), 2587-99.
- Higgins, J.P.T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Available from: <http://www.cochrane-handbook.org/>. Accessed on: June 10, 2011.
- Mujugira, A., Baeten, J. M., Donnell, D., Ndase, P., Mugo, N. R., Barnes, L., et al. (2011). Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. *PLoS One*, 6, (10): e25828.
- Peterson, L., Taylor, D., Roddy, R., Belai, G., Phillips, P., Nanda, K., et al. (2007). Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clinical Trials*, 2, (5): e27.
- University of Washington website. (2011). Pivotal study finds that HIV medications are highly effective as prophylaxis against HIV infection in men and women in Africa. Available from: [http://depts.washington.edu/uwicrc/research/studies/files/PrEP\\_PressRelease-UW\\_13Jul2011.pdf](http://depts.washington.edu/uwicrc/research/studies/files/PrEP_PressRelease-UW_13Jul2011.pdf). Accessed on 2 November 2011.

## Annex 2 - GRADE Table for systematic review of serodiscordant couples

**Author(s):** Caitlin Kennedy, Virginia Tedrow

**Date:** 2012-02-27

**Question:** Should oral emtricitabine (FTC) and/or tenofovir (TDF) be used in heterosexual serodiscordant couples?

**Bibliography:** Baeten et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. NEJM. In Press

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							oral emtricitabine (FTC) and/or tenofovir (TDF)	control	Relative (95% CI)	Absolute		
<b>HIV infection (TDF vs. placebo) (follow-up median 23 months; modified intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	strong association <sup>2</sup>	17/1579 (1.1%)	52/1578 (3.3%)	HR 0.33 (0.19 to 0.56)	22 fewer per 1000 (from 14 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>HIV infection (FTC/TDF vs. placebo) (follow-up median 23 months; modified intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	strong association <sup>3</sup>	13/1576 (0.82%)	52/1578 (3.3%)	HR 0.25 (0.13 to 0.45)	25 fewer per 1000 (from 18 fewer to 29 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Any adverse events (TDF vs. placebo) (follow-up median 23 months; intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1350/1584 (85.2%)	1350/1584 (85.2%)	RR 1.0 (0.9461 to 1.057)	0 fewer per 1000 (from 46 fewer to 49 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Any adverse events (FTC/TDF vs. placebo) (follow-up median 23 months; intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1362/1579 (86.3%)	1350/1584 (85.2%)	RR 1.0065 (0.9524 to 1.0636)	6 more per 1000 (from 41 fewer to 54 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Any grade 3 adverse events (TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	289/1584 (18.2%)	268/1584 (16.9%)	RR 1.0663 (0.9147 to 1.2429)	11 more per 1000 (from 14 fewer to 41 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Any grade 3 adverse events (FTC/TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	293/1579 (18.6%)	268/1584 (16.9%)	RR 1.0816 (0.9284 to 1.26)	14 more per 1000 (from 12 fewer to 44 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Any grade 4 adverse events (TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)</b>												
1 <sup>1</sup>	randomised	no serious	no serious	no serious	no serious	none	34/1584 (2.1%)	39/1584	RR 0.8745 (0.555 to	3 fewer per 1000	⊕⊕⊕⊕	IMPORTANT

	trials	limitations	inconsistency	indirectness	imprecision			(2.5%)	1.3779)	(from 11 fewer to 9 more)	HIGH	
<b>Any grade 4 adverse events (FTC/TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/1579 (2.8%)	39/1584 (2.5%)	RR 1.1282 (0.7372 to 1.7266)	3 more per 1000 (from 6 fewer to 18 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Condom use (TDF vs. placebo) (follow-up median 32 months; sex without condoms with HIV-positive partner)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	27% at baseline 13% at 12 months 9% at 24 months		No difference across study arms (p=0.32)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Condom use (FTC/TDF vs. placebo) (follow-up median 32 months; sex without condoms with HIV-positive partner)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	27% at baseline 13% at 12 months 9% at 24 months		No difference across study arms (p=0.66)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Number of sexual partners (TDF vs. placebo) (follow-up median 32 months; Any report of an outside sexual partner)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	468/1584 (29.5%)	459/1584 (29%)	RR 1.0151 (0.9064 to 1.1369)	4 more per 1000 (from 27 fewer to 40 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Number of sexual partners (FTC/TDF vs. placebo) (follow-up median 32 months; Any report of an outside sexual partner)</b>												
1 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	469/1579 (29.7%)	459/1584 (29%)	RR 1.0193 (0.9102 to 1.1414)	6 more per 1000 (from 26 fewer to 41 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

<sup>1</sup> Baeten et al. 2012 - Partners PrEP

<sup>2</sup> 67% reduction in HIV-1 acquisition vs. placebo

<sup>3</sup> 75% reduction in HIV-1 acquisition vs. placebo



### **Annex 3 - PrEP for serodiscordant couples: values and preferences review of the literature**

There have been few studies conducted among heterosexual individuals and serodiscordant couples examining knowledge and attitudes towards PrEP and related behaviors.

Only one study was conducted among serodiscordant couples.<sup>1</sup> Qualitative, in-depth interviews were conducted with 15 HIV-discordant heterosexual couples recruited from an HIV care clinic in Kisumu, Kenya who expressed a desire to conceive. Most participants responded positively to the idea of PrEP, citing ease of administration as a major advantage.

Several other studies were conducted among heterosexual adults.

One conference abstract from AIDS 2008 presented results from a nationally representative random-digital dial telephone survey of unmarried African-American and white women age 20 to 45 in the United States.<sup>2</sup> Participants were asked about their past sexual practices and whether they would take PrEP if available. Results showed that intention to use PrEP was associated with being African-American (adjusted odds ratio (aOR) = 1.76), having girlfriends who would use PrEP (aOR = 2.20), PrEP being recommended by a doctor (aOR = 1.65), having less than high school education, being unemployed, and having lower income. Expressed intention to take PrEP was highest among women who reported more acts of unprotected vaginal sex in past 90 days, more lifetime and past year sexual partners, having concurrent sexual partners ever or in the past year, and past year injection drug use. It was also higher among women who reported current involvement with a high risk male partner and among women who had tested for HIV.

Another conference abstract presented results from three national surveys with providers and consumers in the United States.<sup>3</sup> While < 4% of consumers reported having a high or medium chance of getting HIV infection, 42% would want to use PrEP. While 81% would recommend that friends or family members at high risk have access to PrEP, only 15% reported knowing something believed to be uninfected but at high risk. 88% of clinicians would prescribe PrEP to at least one risk population.

Another conference abstract presented findings from a semi-structured survey designed to determine acceptability of PrEP, circumcision, and herpes simplex virus suppression among truckers in Hyderabad India.<sup>4</sup> Participants favored and were willing to pay more for herpes suppression compared to PrEP; however, they favored PrEP over circumcision and were willing to pay more for PrEP than circumcision.

Qualitatively, one study conducted focus groups with at-risk African American youth in Atlanta.<sup>5</sup> Participants observed that they were unable to afford, or didn't like taking prescribed oral medication. However, a majority indicated that they would be very interested in utilizing a daily dose of anti-retrovirals for HIV prevention, presuming that PrEP proves to be highly effective, accessible, and free.

Although there have been few studies among serodiscordant couples or heterosexual populations, studies examining knowledge and attitudes towards PrEP and related behaviors among men who have sex with men (MSM) and transgender individuals have been conducted in a variety of locations, including the United States,<sup>6-11</sup> Peru,<sup>12</sup> Thailand<sup>13</sup> and Australia.<sup>14</sup> These studies have surveyed men from a variety of settings, including gay pride events,<sup>6</sup> bath houses,<sup>9</sup> circuit parties,<sup>8</sup> sexually transmitted disease clinics,<sup>6,8</sup> an HIV clinic for the lesbian, gay, bisexual, and transgender community,<sup>10</sup> community settings such as parks, beauty salons, volleyball courts,<sup>12</sup> community-based organizations,<sup>8,12</sup> population-based surveys<sup>8</sup> and the iPrEx trial.<sup>15</sup>

Over time, studies from the United States have reported increasing awareness of PrEP among MSM (16%, 19%, and 36% reported awareness of PrEP from studies published in 2008,<sup>8</sup> 2009<sup>10</sup> and 2011,<sup>9</sup> respectively). An early qualitative study published in 2008 using semi-structured interviews with 72 MSM in the United States suggested that among men who had “virtually no knowledge of PrEP”, reactions to the new product were polarized as either enthusiastic or negative.<sup>11</sup> In this study, positive reactions to PrEP were focused on its user-friendliness and potential benefits for use in serodiscordant relationships; the most common negative reaction to PrEP concerned its potential side-effects.<sup>6</sup> In a more recent qualitative study from Peru, focus group participants said that PrEP was acceptable, but potential sexual risk disinhibition, stigma and discrimination associated with PrEP use, and mistrust of health-care professionals were concerns.<sup>12</sup>

In various quantitative surveys, the number of MSM who said they would consider taking PrEP themselves have ranged from 44%<sup>6</sup> to 70%<sup>7</sup> to 74%<sup>10</sup>. One study from the United States found no association between sexual risk behavior and interest in taking PrEP,<sup>6</sup> while another found that arousal/pleasure barriers to condom use significantly predicted likelihood of PrEP use (odds ratio = 1.71,  $P < 0.05$ )<sup>7</sup>. This same study found that among those who said they would use PrEP, over 35% reported that they would be likely to decrease condom use while on PrEP.<sup>7</sup> Factors affecting PrEP acceptability included efficacy (most studies were conducted before the iPrEx trial results were available), as well as potential side-effects and out of pocket costs.<sup>12</sup>

A study conducted among iPrEx participants in the United States did not focus on values and preferences towards PrEP specifically, but examined experiences with iPrEx staff and common barriers and facilitators to taking PrEP.<sup>15</sup> However, they found that most study participants described iPrEx staff as personable, helpful, and non-judgmental and appreciated health-monitoring provided by staff.<sup>15</sup> Barriers to taking PrEP included stigma of being seen with pills, having co-occurring illnesses, and stress. Facilitators included establishing a routine, bundling PrEP with other medications, and taking the pill in the morning.<sup>15</sup>

### References for Annex 3: PrEP for serodiscordant couples: values and preferences review of the literature

1. Brubaker SG, Darbes L, Bukusi E, Cohen CR. Theoretical acceptability of four interventions to reduce the risk of HIV transmission among HIV discordant couples trying to conceive. In: *International AIDS Society*. Rome, Italy; 2011.
2. Dunkle K, Wingood G, Camp C, DiClemente R. Intention to use pre-exposure prophylaxis among African-American and white women in the United States: results from a national telephone survey. In: *AIDS 2008*. Mexico City, Mexico; 2008.
3. Smith DK, Ntekop E, Pals S. Willingness to use, prescribe, or publicly fund PrEP services: results from 3 national surveys in the United States. In: *AIDS 2010*. Vienna, Austria; 2010.
4. Schneider J, Oruganti G, Pasupneti S, et al. Comparison of acceptability towards circumcision (Circ), pre-exposure prophylaxis (PrEP) and herpes simplex suppression (HSV-S) as novel HIV prevention strategies amongst truck drivers in India In: *5th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. Cape Town, South Africa; 2009.
5. Smith D, Adams MA, Rothenberg R. Attitudes and program preferences regarding pre-exposure prophylaxis (PrEP) among young adults at risk for HIV. In: *International AIDS Society*; 2007.
6. Barash EA, Golden M. Awareness and use of HIV pre-exposure prophylaxis among attendees of a Seattle gay pride event and sexually transmitted disease clinic. *AIDS Patient Care STDS* 2010;24(11):689-91.
7. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. *J Acquir Immune Defic Syndr* 2010;54(5):548-55.
8. Liu AY, Kittredge PV, Vittinghoff E, et al. Limited knowledge and use of HIV post- and pre-exposure prophylaxis among gay and bisexual men. *Journal of Acquired Immune Deficiency Syndromes* 2008;47(2):241-247.
9. Mehta SA, Silvera R, Bernstein K, Holzman RS, Aberg JA, Daskalakis DC. Awareness of post-exposure HIV prophylaxis in high-risk men who have sex with men in New York City. *Sex Transm Infect* 2011;87(4):344-8.
10. Mimiaga MJ, Case P, Johnson CV, Safren SA, Mayer KH. Preexposure antiretroviral prophylaxis attitudes in high-risk Boston area men who report having sex with men: limited knowledge and experience but potential for increased utilization after education. *J Acquir Immune Defic Syndr* 2009;50(1):77-83.
11. Nodin N, Carballo-Diequez A, Ventuneac AM, Balan IC, Remien R. Knowledge and acceptability of alternative HIV prevention bio-medical products among MSM who bareback. *AIDS Care* 2008;20(1):106-15.
12. Galea JT, Kinsler JJ, Salazar X, et al. Acceptability of pre-exposure prophylaxis as an HIV prevention strategy: barriers and facilitators to pre-exposure prophylaxis uptake among at-risk Peruvian populations. *Int J STD AIDS* 2011;22(5):256-62.
13. van Griensven F, Thienkrua W, Sukwicha W, et al. Sex frequency and sex planning among men who have sex with men in Bangkok, Thailand: implications for pre- and post-exposure prophylaxis against HIV infection. *J Int AIDS Soc* 2010;13:13.
14. Poynten IM, Jin F, Prestage GP, Kaldor JM, Imrie J, Grulich AE. Attitudes towards new HIV biomedical prevention technologies among a cohort of HIV-negative gay men in Sydney, Australia. *HIV Med* 2010;11(4):282-8.
15. Liu A, Lubensky D, Koester K, et al. Barriers and facilitators to prevention pill use in iPrEx: Capturing the experience of MSM PrEP study participants in the United States. *Journal of the International Association of Physicians in AIDS Care* 2010;9(4):261-262.

## **Annex 4 - Pre-exposure prophylaxis (PrEP) for men and transgender women who have sex with men (MSM and TG): a systematic review**

**September 19, 2011**

### **Background**

More than 34 million people globally are living with HIV (UNAIDS, 2010). A number of prevention methods are available, from condoms to male circumcision, from prevention of mother-to-child transmission to clean needles, but to date these approaches have not been sufficient to stop the epidemic. In 2009 alone, an estimated 2.7 million people became newly infected (UNAIDS, 2010). Additional safe and effective approaches to HIV prevention are urgently needed.

Men and transgender women who have sex with men (MSM and TG) have a disproportionate burden of HIV in most countries in the world, even in many countries with generalized HIV epidemics. Worldwide, their odds of being infected with HIV are 19.3 times higher than those for others (Baral et al., 2007). Clearly, existing methods of HIV prevention are not sufficient for MSM and TG. Biomedical prevention has shown promise. Male circumcision has proved effective in protecting heterosexual men who are exposed to HIV during penile-vaginal intercourse, and a vaginal gel has shown some effectiveness in protecting women who are exposed by vaginal intercourse. Pre-exposure prophylaxis (PrEP) is the first biomedical intervention that has proved effective in providing additional protection to men who have unprotected rectal exposure to HIV.

PrEP is the use of an antiretroviral drug to block the acquisition of HIV infection by uninfected people. Proof of concept has long been established in the laboratory by animal studies and in real world application by the prevention of mother-to-child transmission and post-exposure prophylaxis. The safety of the drugs being considered for PrEP, tenofovir and emtricitabine, has been established through their use for treatment and in safety trials in uninfected people (Peterson et al., 2007). Five trials of effectiveness (Phase IIb and Phase III) have been started since 2005. These focus on effectiveness of oral PrEP among injection drug users, serodiscordant couples, heterosexual women and high risk men who have sex with men.

This systematic review examined evidence for the following PICO question: Should oral emtricitabine (FTC 200mg) and tenofovir (TDF 300mg) be used for HIV prevention among high risk men and transgender women who have sex with men?

### **Methods**

#### ***PICO question***

**PICO 1:** Should oral emtricitabine (FTC 200mg) and tenofovir (TDF 300mg) be used for HIV prevention among high risk men and transgender women who have sex with men?

**P:** High risk men and transgender women who have sex with men

**I:** Oral emtricitabine (FTC 200mg) and tenofovir (TDF 300mg)

**C:** Placebo

**O:** (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, (4) condom use, and 5) number of sexual partners

### ***Inclusion criteria***

To be included in the review, an article had to meet the following criteria:

- 1) Randomized controlled trial evaluating the use of oral emtricitabine (FTC 200mg) and tenofovir (TDF 300mg) to prevent HIV infection among MSM and TG participants.
- 2) Measured one or more of the following key outcomes: (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, 4) condom use, and 5) number of sexual partners.
- 3) Published in a peer-reviewed journal, or presented as an abstract at a scientific conference, between January 1, 1990 and June 15, 2011.

No restrictions were placed based on location of the intervention. No language restrictions were used on the search. Articles in languages other than English were translated where necessary.

Following the GRADE approach, when direct evidence from MSM and TG populations was not available for one or more of the key outcomes, indirect evidence from other populations (heterosexual men or women) was used instead, but downgraded for indirectness. If evidence from other populations was not available, evidence from non-randomized but controlled studies was used instead, but also downgraded for directness.

### ***Search strategy***

The following electronic databases were searched using the date ranges January 1, 1990 to June 15, 2011: PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and EMBASE. Secondary reference searching was conducted on all studies included in the review. Further, selected experts in the field were contacted to identify additional articles not identified through other search methods.

Abstracts from the following conferences were searched from January 1, 1990 to June 15, 2011: International AIDS Conference (IAC), IAS Conference on HIV Pathogenesis, Treatment, and Prevention (IAS), and Conference on Retroviruses and Opportunistic Infections (CROI).

### ***Search terms***

The following terms were entered into all computer databases:

(“men who have sex with men” or MSM or transgender or TG or “gay men”) AND (“pre-exposure prophylaxis” or PrEP or emtricitabine or tenofovir or Truvada or FTC or TDF) AND (HIV OR AIDS)

### ***Screening abstracts***

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened by two members of the study staff. Full text articles were

obtained for all selected abstracts and both reviewers independently assessed all full-text articles for eligibility to determine final study selection. Differences were resolved through consensus.

Articles not meeting the inclusion criteria for the review, but presenting potentially interesting background information relevant to PrEP among MSM and TG, including review articles, qualitative studies, cost or cost-effectiveness analyses, or descriptions of interventions without an evaluation component, were included in an annotated bibliography of additional articles.

### ***Data extraction and management***

Data were extracted independently by two reviewers using standardized data extraction forms. Differences in data extraction were resolved through consensus and referral to a senior team member from WHO when necessary. Study authors were contacted when additional information or data were needed.

The following information was gathered from each included study:

- Study identification: Author(s); type of citation; year of publication
- Study description: Study objectives; location; population characteristics; description of the intervention; study design; sample size; follow-up periods and loss to follow-up
- Outcomes: Analytic approach; outcome measures; comparison groups; effect sizes; confidence intervals; significance levels; conclusions; limitations

Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook, chapter 8.5 – Higgins & Green, 2011). This tool assesses random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) blinding of outcome assessment (detection bias), incomplete outcome data addressed (attrition bias), incomplete outcome data, and selective reporting (reporting bias).

Methodological components of the studies were assessed and classified as high, low, or uncertain risk of bias.

### ***Data analysis***

Data were analyzed according to the data extraction categories and outcomes listed above. If multiple studies reported the same outcome, meta-analysis would have been conducted using random-effects models to combine odds ratios with the program Comprehensive Meta-Analysis (CMA). Data were summarized in GRADE evidence profiles, summary of finding tables, and risk/benefit tables.

## **Results**

Our initial database search yielded 206 citations and 84 conference abstracts; one additional study was identified through other means, such as searching through the reference lists of relevant articles (Figure 1). One randomized trial was deemed eligible for inclusion in our review.

Although the three remaining abstracts were determined to meet the inclusion criteria, all three were interim analyses of ongoing trials and were thus judged to be of less certain quality

than the published study, so they were not fully coded or included in GRADE tables. Since all three abstracts included only data on adverse events and not other outcomes of interest, their preliminary results are presented in this section along with the one included study.

The one study that met all inclusion criteria was the iPrEx trial (Grant et al., 2010). This study was a randomized controlled trial to evaluate the safety and efficacy of once-daily oral FTC-TDF as compared with placebo for the prevention of HIV acquisition among MSM-TG. The trial was conducted in 6 countries: Peru, Ecuador, South Africa, Brazil, Thailand, and the United States. All study participants were born male, although 29 (1%) reported their current gender identity as female. Participants' ages ranged from 18 to 67 years.

Using the Cochrane Risk of Bias tool, the study was judged to have low risk of bias across all of the following categories: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data addressed (attrition bias), selective reporting (reporting bias), and other biases. The study was stopped early for evidence of benefit, which may overestimate treatment effects; however, as this was a multi-country study judged to have low risk of bias on all other criteria, it was not downgraded for this reason, and was considered high quality.

The study measured all five key outcomes for this review: 1) HIV infection, 2) Any adverse event, 3) Any stage 3 or 4 adverse event, 4) Condom use, and 5) Number of sexual partners.

### ***HIV infection***

Incident HIV infection was significantly reduced among participants in the FTC-TDF study arm as compared to the control arm using both an intention-to-treat analysis and a modified intention-to-treat excluding participants who had HIV RNA detected at baseline. In the intention-to-treat analysis, there were 38 incident cases of HIV infection out of 1251 participants in the FTC-TDF study arm and 72 incident HIV infections out of 1248 participants in the control group, resulting in a hazard ratio of 0.53 (95% CI 0.36-0.78,  $p=0.001$ ). In the modified intention-to-treat analysis, there were 36 incident cases of HIV in the FTC-TDF group (N=1251) and 64 incident cases of HIV in the control group (N=1248). For this analysis, the hazard ratio of HIV infection comparing those in the FTC-TDF group to the control was 0.56 (95% CI 0.37-0.85,  $p=0.005$ ), thus showing a 44% reduction in the relative risk of HIV infection.

### ***Any adverse event***

There was no statistically significant difference in reported adverse events between the two study arms. In the FTC-TDF arm, 867 out of 1251 patients (69%) reported having any adverse event compared to 877 out of 1248 patients (70%) in the control group. The relative risk of having any adverse event comparing the intervention to control group was 0.99 (95% CI 0.94-1.04), which was not statistically significant.

One additional abstract provided information on any adverse event. Mutua et al. (2010) found that both dose regimens had similar rates of adverse events.

### ***Any stage 3 or 4 adverse event***

Both study arms also reported similar rates of stage 3 and 4 adverse events. In the FTC-TDF study arm, 151 out of 1251 patients (12%) reported having a grade 3 or 4 adverse event compared to 164 out of 1248 patients (13%) in the control arm. The relative risk of having any grade 3 or 4 adverse event was 0.92 (95% CI 0.75-1.13) comparing the intervention to control arm, thus showing no statistical difference between the two groups.

The three additional abstracts provided information on any stage 3 or 4 adverse event. Grohskopf et al. (2010) found no statistically significant differences between TDF and placebo groups in any grade 3 or 4 adverse event (clinical or lab). Mutua et al. (2010) found that all adverse events were mild or moderate with most judged unlikely related or not related to study drug/placebo; no drug-related serious adverse events were reported. Liu et al. (2011) found that overall, 10 participants reported fractures during follow-up: 6 in the TDF group and 4 in the placebo group ( $p = 0.75$ ); all were trauma-related and assessed as not related to study drug.

### *Condom use*

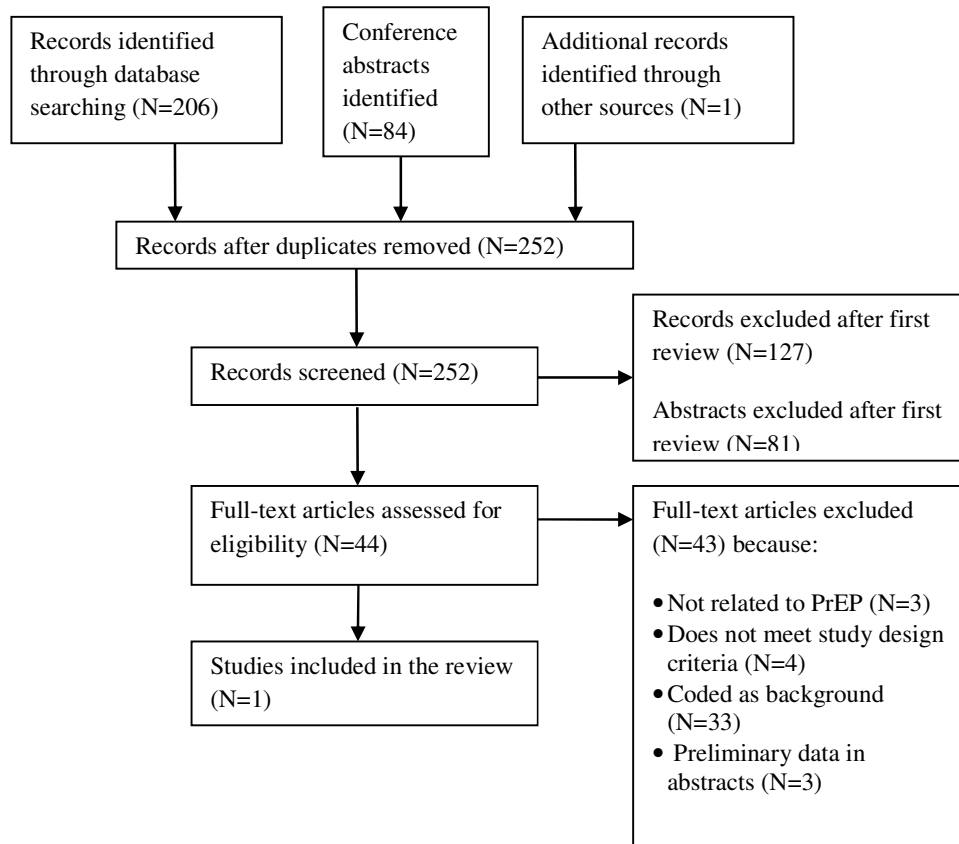
The study found that both groups reported increased condom use (defined as the percent of partners using condoms during receptive intercourse) over the course of the intervention, but that differences in condom use rates between the FTC-TDF arm (N=1251 at baseline) and control arm (N=1248) did not differ significantly ( $p=0.36$ ). To examine this relationship, a linear mixed regression model was fitted with a random intercept and fixed effects for treatment visit and treatment by visit interaction. The p-value is from a Wald test of the treatment by visit interaction which corresponds to whether or not there is a difference during the study period between the FTC-TDF and control groups. The description of the analysis conducted was received as correspondence from the study authors and was not included in the original publication.

### *Number of sexual partners*

In both groups, the number of receptive sexual intercourse partners declined from baseline to follow-up over the course of the study; however, there was no significant difference between the number of partners reported in each study group at each time point ( $p=0.97$ ). Results were calculated by fitting a linear mixed regression model with a random intercept and fixed effects for treatment visit and treatment by visit interaction. The p-value is from a Wald test of the treatment by visit interaction which corresponds to whether or not there is a difference during the study period between the arms in the number of sexual partners (total male partners at over a 12 week recall period with whom the participant had oral or anal sex). These results and a description of the analysis conducted were received as correspondence from the study authors and were not included in the original publication.



**Figure 1: Disposition of citations during the search and screening process**



**Table 1: Risk-benefit table**

Factor	Explanation / Evidence	Judgment
<b>Quality of Evidence</b>	One multi-country RCT without serious limitations. Additional studies from other populations at various stages of completion.	<b>High</b>
<b>Balance of Benefits vs. Harms</b>	<p><b><i>HIV infection</i></b> Oral PrEP was associated with reduced risk of HIV in both intention-to-treat analysis (HR: 0.53, 95% CI 0.36-0.78, p=0.001) and modified intention-to-treat analysis (HR: 0.56, 95% CI 0.37-0.85, p=0.005).</p> <p><b><i>Adverse events</i></b> There was no significant difference in reported adverse events between the FTC-TDF and control arms for either any adverse event (RR: 0.99, 95% CI 0.94-1.04) or grade 3 and 4 adverse events (RR: 0.92, 95% CI 0.75-1.13). Preliminary analyses from ongoing studies show no major differences in adverse events across treatment and control groups.</p> <p><b><i>Condom use</i></b> Both the FTC-TDF and control study arms reported increased condom use (defined as the percent of partners using condoms during receptive intercourse) from baseline to follow-up over the course of the study; however, there was no significant difference in condom use rates between study arms over time (p=0.36).</p> <p><b><i>Number of sexual partners</i></b> Both the FTC-TDF and control study arms reported reduced number of receptive sexual intercourse partners from baseline to follow-up over the course of the study; however, there was no significant difference in the reported number of sexual partners between study arms over time (p=0.97).</p>	<b>Benefits outweigh harms</b>
<b>Values and Preferences</b>	Studies examining MSM-TG knowledge and attitudes towards PrEP have been conducted in several settings. U.S. studies report increasing awareness of PrEP among MSM over time. Between 44% and 74% of MSM said they would consider taking PrEP themselves across studies. Positive aspects of PrEP include user-friendliness and potential benefits for use in serodiscordant relationships. Concerns include potential side-effects, potential sexual risk disinhibition, stigma and discrimination associated with PrEP use, and mistrust of health-care professionals. Factors affecting PrEP acceptability included efficacy (most studies were conducted before iPrEx trial results), potential side-effects and out of pocket costs.	<b>Acceptable to many MSM-TG</b>
<b>Resource Use</b>	One cost-effectiveness study from Australia estimated that if continuous PrEP was 90% effective and the program covered only HIV-negative MSM having high risk sex, it would cost \$47,745 per quality adjusted life year (QALY) gained	<b>Consideration in certain settings</b>

	<p>(Anderson &amp; Cooper, 2009).</p> <p>Another cost-effectiveness study found PrEP to be cost-effective under 75% of the 80 scenarios tested at a threshold of US\$50,000 per QALY gained (Desai et al. 2008).</p> <p>Another cost-effectiveness study from the USA estimated that if PrEP was 90% effective and the program covered only HIV-negative MSM having high risk sex, it would cost US\$107,000 per QALY gained. If PrEP was 50% effective, it would cost US\$298,000 per QALY gained. Sensitivity analyses showed that the cheaper and more efficacious PrEP is and the more high risk the population, the more cost-effective it will be, with a range of estimates from cost-saving to over US\$300,000 per QALY saved (Paltiel et al., 2009).</p> <p>Cost-effectiveness estimates vary widely depending on model parameter estimates, including efficacy, cost of PrEP, and HIV incidence and age of the target population. Results range from being cost-saving to costing over US\$300,000 per QALY saved.</p>	
<b>Feasibility</b>	<p>Oral PrEP for MSM has proven feasible in various trial settings. Issues of criminalization, stigma and discrimination, and violence should be considered during implementation, especially where MSM-TG behavior is illegal.</p>	<b>Consideration in certain settings</b>

## References for annex 4 - Pre-exposure prophylaxis (PrEP) for men and transgender women who have sex with men (MSM and TG): a systematic review

- Anderson, J., & Cooper, D. (2009). Cost-effectiveness of pre-exposure prophylaxis for HIV in an MSM population. *HIV Medicine, 10*: 39.
- Baral, S., Sifakis, F., Cleghorn, F., & Beyrer, C. (2007). Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000–2006: A systematic review. *PLoS Med, 4* (12), e339.
- Grant, R. M., Lama, J. R., Anderson, P. L., McMahan, V., Liu, A. Y., Vargas, L., et al. (2010). Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *NEJM, 363*, (27), 2587-99.
- Grohskopf, L., Gvetadze, R., Pathak, S., O'Hara, B., Mayer, K., Liu, A., et al. (2010). Preliminary analysis of biomedical data from the phase II clinical safety trial of tenofovir disoproxil fumarate (TDF) for HIV-1 pre-exposure prophylaxis (PrEP) among U.S. men who have sex with men (MSM). Abstract no. FRLBC102. International XVIII International AIDS Conference, Vienna, Austria. (<http://pag.aids2010.org/Abstracts.aspx?AID=17777>)
- Higgins, J.P.T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Available from: <http://www.cochrane-handbook.org/>. Accessed on: June 10, 2011.
- Liu, A., Vittinghoff, E., Irby, R., Mulligan, K., Sellmeyer, D., Mayer, K., et al. (2011). BMD Loss in HIV<sup>-</sup> Men Participating in a TDF PrEP Clinical Trial in San Francisco. 18th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, USA.
- Mutua, G., Sanders, E.J., Kamali, A., Kibengo, F., Mugo, P., Anzala, O., et al. (2010). Safety and adherence to intermittent emtricitabine/tenofovir for HIV pre-exposure prophylaxis (PrEP) in Kenya and Uganda. Abstract no. MOPE0369. International XVIII International AIDS Conference, Vienna, Austria. (<http://pag.aids2010.org/Abstracts.aspx?AID=2521>).
- Peterson, L., Taylor, D., Roddy, R., Belai, G., Phillips, P., Nanda, K., et al. (2007). Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clinical Trials, 2*, (5): e27.
- UNAIDS. (2010). Global report: UNAIDS report on the global AIDS epidemic.

## Annex 5 - GRADE table for systematic review of MSM/TG

**Author(s):** Caitlin Kennedy, Virginia Tedrow

**Date:** 2011-07-15

**Question:** Should emtricitabine (FTC 200mg) and tenofovir (TDF 300mg) be used in high risk men and transgender women who have sex with men?

**Settings:** Lima and Iquitos, Peru; Guayaquil, Ecuador; Cape Town, South Africa; Rio de Janeiro and Sao Paulo, Brazil; Chiang Mai, Thailand; Boston and San Francisco, USA

**Bibliography:** Grant, R. M., Lama, J. R., Anderson, P. L., McMahan, V., Liu, A. Y., Vargas, L., et al. (2010). Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. NEJM, 363, (27), 2587-99.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Emtricitabine (FTC 200mg) and tenofovir (TDF 300mg)	Control	Relative (95% CI)	Absolute		
<b>HIV infection (follow-up median 1.2 years; assessed with: intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/1251 (3%)	72/1248 (5.8%)	HR 0.53 (0.36 to 0.78)	27 fewer per 1000 (from 12 fewer to 37 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>HIV infection (follow-up median 1.2 years; assessed with: modified intention to treat analysis)</b>												
1 <sup>1</sup>	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/1251 (2.9%)	64/1248 (5.1%)	HR 0.56 (0.37 to 0.85)	22 fewer per 1000 (from 8 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Any adverse events (follow-up median 1.2 years)</b>												
1 <sup>1</sup>	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	867/1251 (69.3%)	877/1248 (70.3%)	RR 0.99 (0.94 to 1.04)	7 fewer per 1000 (from 42 fewer to 28 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Any grade 3 or 4 adverse events (follow-up median 1.2 years)</b>												
1 <sup>1</sup>	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	151/1251 (12.1%)	164/1248 (13.1%)	RR 0.92 (0.75 to 1.13)	11 fewer per 1000 (from 33 fewer to 17 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Condom use (percent of receptive anal partners with which condoms were used) (follow-up median 1.2 years)</b>												
1 <sup>1</sup>	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1251 <sup>2</sup>	1248 <sup>2</sup>	p=0.36 <sup>3</sup>	-	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Number of sexual partners (mean number of anal receptive partners) (follow-up median 1.2 years)</b>												
1 <sup>1</sup>	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1251 <sup>2</sup>	1248 <sup>2</sup>	P=0.97 <sup>4</sup>	-	⊕⊕⊕⊕ HIGH	IMPORTANT

<sup>1</sup> Grant et al. 2010 - iPrEx study

<sup>2</sup> Total baseline sample size

<sup>3</sup>This was a comparison between the two study arms of the percent of partners using condoms during receptive anal intercourse. The results were calculated by fitting a linear mixed regression model with a random intercept and fixed effects for treatment visit and treatment by visit interaction. The p-value is from a Wald test of the treatment by visit interaction which corresponds to whether or not there is a difference during the study period between the arms in the percent of partners using condoms during receptive anal intercourse.

<sup>4</sup>This was a comparison between the two study arms of the total number of sexual partners reported. Results were calculated by fitting a linear mixed regression model with a random intercept and fixed effects for treatment visit and treatment by visit interaction. The p-value is from a Wald test of the treatment by visit interaction which corresponds to whether or not there is a difference during the study period between the arms in the number of sexual partners (total male partners at over a 12 week recall period with whom the participant had oral or anal sex).

## **Annex 6 – PrEP for MSM/TG: values and Preferences review of the literature**

**September 7, 2011**

Studies among MSM-TG examining knowledge and attitudes towards PrEP and related behaviors have been conducted in a variety of locations, including the United States,<sup>1-6</sup> Peru,<sup>7</sup> Thailand<sup>8</sup> and Australia.<sup>9</sup> These studies have surveyed men from a variety of settings, including gay pride events,<sup>1</sup> bath houses,<sup>4</sup> circuit parties,<sup>3</sup> sexually transmitted disease clinics,<sup>1,3</sup> an HIV clinic for the lesbian, gay, bisexual, and transgender community,<sup>5</sup> community settings such as parks, beauty salons, volleyball courts,<sup>7</sup> community-based organizations,<sup>3,7</sup> population-based surveys<sup>3</sup> and the iPrEx trial.<sup>10</sup>

Over time, studies from the United States have reported increasing awareness of PrEP among MSM (16%, 19%, and 36% reported awareness of PrEP from studies published in 2008,<sup>3</sup> 2009<sup>5</sup> and 2011,<sup>4</sup> respectively). An early qualitative study published in 2008 using semi-structured interviews with 72 MSM in the United States suggested that among men who had “virtually no knowledge of PrEP”, reactions to the new product were polarized as either enthusiastic or negative.<sup>6</sup> In this study, positive reactions to PrEP were focused on its user-friendliness and potential benefits for use in serodiscordant relationships; the most common negative reaction to PrEP concerned its potential side-effects.<sup>6</sup> In a more recent qualitative study from Peru, focus group participants said that PrEP was acceptable, but potential sexual risk disinhibition, stigma and discrimination associated with PrEP use, and mistrust of health-care professionals were concerns.<sup>7</sup>

In various quantitative surveys, the number of MSM who said they would consider taking PrEP themselves have ranged from 44%<sup>1</sup> to 70%<sup>2</sup> to 74%<sup>5</sup>. One study from the United States found no association between sexual risk behavior and interest in taking PrEP,<sup>1</sup> while another found that arousal/pleasure barriers to condom use significantly predicted likelihood of PrEP use (odds ratio = 1.71,  $P < 0.05$ )<sup>2</sup>. This same study found that among those who said they would use PrEP, over 35% reported that they would be likely to decrease condom use while on PrEP.<sup>2</sup> Factors affecting PrEP acceptability included efficacy (most studies were conducted before the iPrEx trial results were available), as well as potential side-effects and out of pocket costs.<sup>7</sup>

A study conducted among iPrEx participants in the United States did not focus on values and preferences towards PrEP specifically, but examined experiences with iPrEx staff and common barriers and facilitators to taking PrEP.<sup>10</sup> However, they found that most study participants described iPrEx staff as personable, helpful, and non-judgmental and appreciated health-monitoring provided by staff.<sup>10</sup> Barriers to taking PrEP included stigma of being seen with pills, having co-occurring illnesses, and stress. Facilitators included establishing a routine, bundling PrEP with other medications, and taking the pill in the morning.<sup>10</sup>

## References for Annex 6 – PrEP for MSM/TG: values and Preferences review of the literature

1. Barash EA, Golden M. Awareness and use of HIV pre-exposure prophylaxis among attendees of a Seattle gay pride event and sexually transmitted disease clinic. *AIDS Patient Care STDS* 2010;24(11):689-91.
2. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. *J Acquir Immune Defic Syndr* 2010;54(5):548-55.
3. Liu AY, Kittredge PV, Vittinghoff E, et al. Limited knowledge and use of HIV post- and pre-exposure prophylaxis among gay and bisexual men. *Journal of Acquired Immune Deficiency Syndromes* 2008;47(2):241-247.
4. Mehta SA, Silvera R, Bernstein K, Holzman RS, Aberg JA, Daskalakis DC. Awareness of post-exposure HIV prophylaxis in high-risk men who have sex with men in New York City. *Sex Transm Infect* 2011;87(4):344-8.
5. Mimiaga MJ, Case P, Johnson CV, Safren SA, Mayer KH. Preexposure antiretroviral prophylaxis attitudes in high-risk Boston area men who report having sex with men: limited knowledge and experience but potential for increased utilization after education. *J Acquir Immune Defic Syndr* 2009;50(1):77-83.
6. Nodin N, Carballo-Diequez A, Ventuneac AM, Balan IC, Remien R. Knowledge and acceptability of alternative HIV prevention bio-medical products among MSM who bareback. *AIDS Care* 2008;20(1):106-15.
7. Galea JT, Kinsler JJ, Salazar X, et al. Acceptability of pre-exposure prophylaxis as an HIV prevention strategy: barriers and facilitators to pre-exposure prophylaxis uptake among at-risk Peruvian populations. *Int J STD AIDS* 2011;22(5):256-62.
8. van Griensven F, Thienkrua W, Sukwicha W, et al. Sex frequency and sex planning among men who have sex with men in Bangkok, Thailand: implications for pre- and post-exposure prophylaxis against HIV infection. *J Int AIDS Soc* 2010;13:13.
9. Poynten IM, Jin F, Prestage GP, Kaldor JM, Imrie J, Grulich AE. Attitudes towards new HIV biomedical prevention technologies among a cohort of HIV-negative gay men in Sydney, Australia. *HIV Med* 2010;11(4):282-8.
10. Liu A, Lubensky D, Koester K, et al. Barriers and facilitators to prevention pill use in iPrEx: Capturing the experience of MSM PrEP study participants in the United States. *Journal of the International Association of Physicians in AIDS Care* 2010;9(4):261-262.



## Annex 7: Members of external groups

### WHO Steering Group

- **Kevin O'Reilly**
- **Ying-Ru Lo**
- **Florence Koechlin**
- **Rachel Baggaley**
- **Marco Vitoria**

### Guidelines Development Group

- **Jorge Beloqui**, Director, Grupo GIV, Sao Paulo, Brasil (civil society, MSM, persons living with HIV)
- **Carlos Caceres**, Profesor Principal de Salud Pública, Universidad Peruana Cayetano Heredia, Director, Instituto de Estudios en Salud, Sexualidad y Desarrollo Humano, Lima, Peru (academic, research, epidemiology, MSM)
- **Peter Cherutich**, Head, HIV Prevention, National AIDS & STIs Control Programme, Ministry of Health, Nairobi, Kenya (government, programme implementation)
- **Catherine Hankins**, Deputy Director, Science, Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands (research, epidemiology)
- **Mark Dybul**, Distinguished Scholar, O'Neill Institute for National and Global Health Law, Georgetown University, Washington, DC, USA (nongovernmental, epidemiology, advocacy, research into action)
- **Smarajit Jana**, consultant DMSC, Kolkata, India (NGO, civil society, sex work)
- **Helen Rees**, Executive Director, Wits Reproductive Health and HIV Institute (WRHI), University of the Witwatersrand, Johannesburg, South Africa (research, reproductive health)
- **Petchsri Sirirund**, Department of Diseases Control, Ministry of Public Health, Bangkok, Thailand (government, programme development and implementation, monitoring and evaluation)
- **Dawn Smith**, Biomedical Interventions Implementation Officer, Epidemiology Branch, Division of HIV/AIDS Prevention, U.S. Centers for Disease Control, Atlanta, GA, USA. (government, epidemiology, research, programme development and implementation)

### External Review Group

- **Pedro Chequer**, Coordenador do UNAIDS no Brasil, Brasilia (international organization, programme development and implementation)

- **Adeeba Kamarulzaman**, Director, Centre of Excellence for Research in AIDS, University of Malaya, Kuala Lumpur, Malaysia (academic, research, civil society, IDU)
- **Mean Chhi Vun**, Director, National Center for HIV/AIDS Dermatology and STD, Phnom Penh, Cambodia (government, epidemiology, programme development)
- **Lynn Paxton**, Antiretroviral Prophylaxis and Microbicides Team, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, U.S.A. (government, epidemiology, research, programme development and implementation)
- **Brian Pazvakavambwa**, Team Leader for the HIV/AIDS Area of Work in the Inter-Country Support Team for Eastern and Southern Africa, WHO AFRO (international organization, epidemiology, programme development and implementation)

WHO/HIV/2012.20

© World Health Organization 2012