HIV/AIDS Programme

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

World Health Organization

HIV/AIDS Programme

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

World Health Organization

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)

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[1] 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

1 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/prep_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[1] 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)*.

1 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[1] 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

1 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/. 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[1]

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.

1 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/.)

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.[1]

1 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. 6th 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/
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

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

ISBN 978 92 4 1503884