

**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**

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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/mm³ (IQR 375–662), 80% had CD4 counts \geq 350 cells/mm³, and median plasma HIV-1 RNA level was 3.9 log₁₀ 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

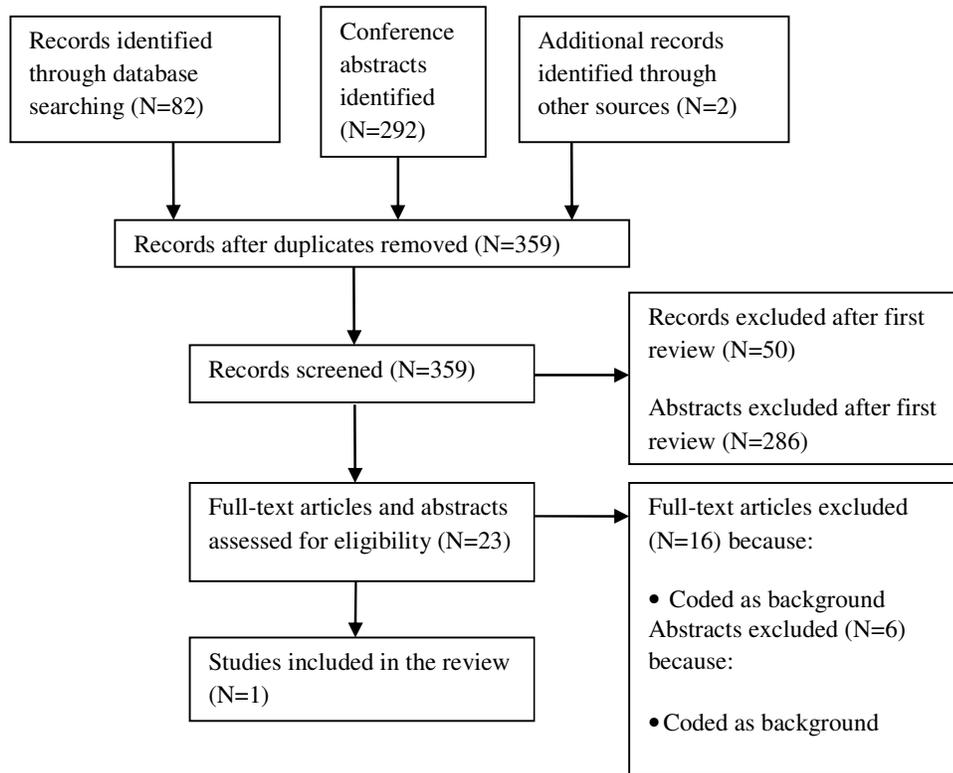


Table 1: Risk-benefit table

Factor	Explanation / Evidence	Judgment
Quality of Evidence	One multi-country RCT without serious limitations. Additional studies from other populations at various stages of completion.	High
Balance of Benefits vs. Harms	<p><i>HIV infection</i> 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<0.001] and 75% for FTC/TDF (HR: 0.25, 95% CI 0.13-0.45, p<0.001). These HIV-1 protective effects of TDF and FTC/TDF were not statistically different by sex.</p> <p><i>Adverse events</i> 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><i>Condom use</i> 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><i>Number of sexual partners</i> 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>	Benefits outweigh harms
Values and Preferences	Although few studies have examined values and preferences around PrEP for serodiscordant couples, existing research indicates acceptability.	Acceptable
Resource Use	<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"> - Cost per infection averted was between US\$6,000 and \$66,000 when PrEP was always used - Cost per QALY saved was \$260-\$4,900 <p>Using “more typical” data on risk behavior</p>	Consideration in certain settings

	<ul style="list-style-type: none"> - Cost per infection averted was between ~\$0 (break-even) and \$26,000 when PrEP was always used - Cost per QALY saved was -\$200 (cost-saving) to \$1,900 <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>	
Feasibility	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.	Consideration in certain settings

References for Annex 1: systematic review of serodiscordant couples

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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		
HIV infection (TDF vs. placebo) (follow-up median 23 months; modified intention to treat analysis)												
1 ¹	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	strong association ²	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
HIV infection (FTC/TDF vs. placebo) (follow-up median 23 months; modified intention to treat analysis)												
1 ¹	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	strong association ³	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
Any adverse events (TDF vs. placebo) (follow-up median 23 months; intention to treat analysis)												
1 ¹	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
Any adverse events (FTC/TDF vs. placebo) (follow-up median 23 months; intention to treat analysis)												
1 ¹	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
Any grade 3 adverse events (TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)												
1 ¹	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
Any grade 3 adverse events (FTC/TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)												
1 ¹	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
Any grade 4 adverse events (TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)												
1 ¹	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	
Any grade 4 adverse events (FTC/TDF vs. placebo) (follow-up median 32 months; intention to treat analysis)												
1 ¹	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
Condom use (TDF vs. placebo) (follow-up median 32 months; sex without condoms with HIV-positive partner)												
1 ¹	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
Condom use (FTC/TDF vs. placebo) (follow-up median 32 months; sex without condoms with HIV-positive partner)												
1 ¹	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
Number of sexual partners (TDF vs. placebo) (follow-up median 32 months; Any report of an outside sexual partner)												
1 ¹	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
Number of sexual partners (FTC/TDF vs. placebo) (follow-up median 32 months; Any report of an outside sexual partner)												
1 ¹	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

¹ Baeten et al. 2012 - Partners PrEP

² 67% reduction in HIV-1 acquisition vs. placebo

³ 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.¹ 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.² 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.³ 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.⁴ 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.⁵ 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,⁶⁻¹¹ Peru,¹² Thailand¹³ and Australia.¹⁴ These studies have surveyed men from a variety of settings, including gay pride events,⁶ bath houses,⁹ circuit parties,⁸ sexually transmitted disease clinics,^{6,8} an HIV clinic for the lesbian, gay, bisexual, and transgender community,¹⁰ community settings such as parks, beauty salons, volleyball courts,¹² community-based organizations,^{8,12} population-based surveys⁸ and the iPrEx trial.¹⁵

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 2008,⁸ 2009¹⁰ and 2011,⁹ 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.¹¹ 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.⁶ 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.¹²

In various quantitative surveys, the number of MSM who said they would consider taking PrEP themselves have ranged from 44%⁶ to 70%⁷ to 74%¹⁰. One study from the United States found no association between sexual risk behavior and interest in taking PrEP,⁶ while another found that arousal/pleasure barriers to condom use significantly predicted likelihood of PrEP use (odds ratio = 1.71, $P < 0.05$)⁷. 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.⁷ 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.¹²

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.¹⁵ However, they found that most study participants described iPrEx staff as personable, helpful, and non-judgmental and appreciated health-monitoring provided by staff.¹⁵ 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.¹⁵

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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

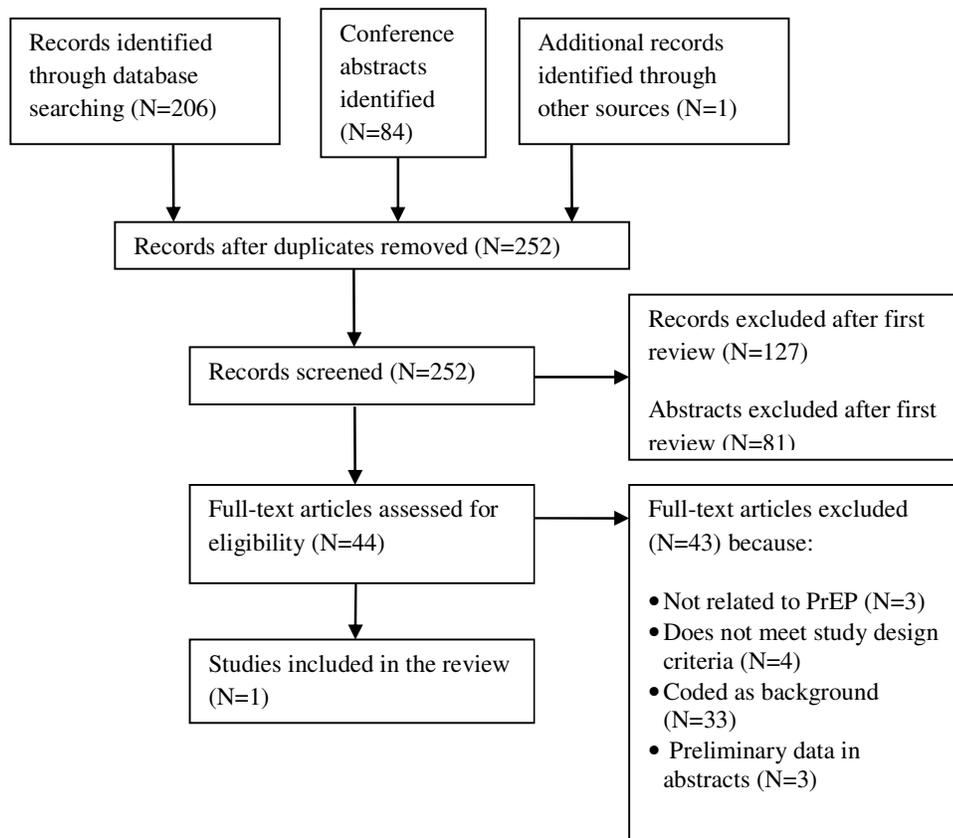


Table 1: Risk-benefit table

Factor	Explanation / Evidence	Judgment
Quality of Evidence	One multi-country RCT without serious limitations. Additional studies from other populations at various stages of completion.	High
Balance of Benefits vs. Harms	<p><i>HIV infection</i> 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><i>Adverse events</i> 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><i>Condom use</i> 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><i>Number of sexual partners</i> 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>	Benefits outweigh harms
Values and Preferences	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.	Acceptable to many MSM-TG
Resource Use	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	Consideration in certain settings

	<p>(Anderson & 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>	
Feasibility	<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>	Consideration in certain settings

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

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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		
HIV infection (follow-up median 1.2 years; assessed with: intention to treat analysis)												
1 ¹	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
HIV infection (follow-up median 1.2 years; assessed with: modified intention to treat analysis)												
1 ¹	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
Any adverse events (follow-up median 1.2 years)												
1 ¹	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
Any grade 3 or 4 adverse events (follow-up median 1.2 years)												
1 ¹	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
Condom use (percent of receptive anal partners with which condoms were used) (follow-up median 1.2 years)												
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1251 ²	1248 ²	p=0.36 ³	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of sexual partners (mean number of anal receptive partners) (follow-up median 1.2 years)												
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1251 ²	1248 ²	P=0.97 ⁴	-	⊕⊕⊕⊕ HIGH	IMPORTANT

¹ Grant et al. 2010 - iPrEx study

² Total baseline sample size

³This 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.

⁴This 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,¹⁻⁶ Peru,⁷ Thailand⁸ and Australia.⁹ These studies have surveyed men from a variety of settings, including gay pride events,¹ bath houses,⁴ circuit parties,³ sexually transmitted disease clinics,^{1,3} an HIV clinic for the lesbian, gay, bisexual, and transgender community,⁵ community settings such as parks, beauty salons, volleyball courts,⁷ community-based organizations,^{3,7} population-based surveys³ and the iPrEx trial.¹⁰

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 2008,³ 2009⁵ and 2011,⁴ 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.⁶ 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.⁶ 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.⁷

In various quantitative surveys, the number of MSM who said they would consider taking PrEP themselves have ranged from 44%¹ to 70%² to 74%⁵. One study from the United States found no association between sexual risk behavior and interest in taking PrEP,¹ while another found that arousal/pleasure barriers to condom use significantly predicted likelihood of PrEP use (odds ratio = 1.71, $P < 0.05$)². 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.² 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.⁷

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.¹⁰ However, they found that most study participants described iPrEx staff as personable, helpful, and non-judgmental and appreciated health-monitoring provided by staff.¹⁰ 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.¹⁰

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

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