

## Review

# Antiretroviral-based HIV-1 prevention: antiretroviral treatment and pre-exposure prophylaxis

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Antiretroviral-based HIV-1 prevention strategies – including antiretroviral treatment (ART) to reduce the infectiousness of individuals with HIV-1 and oral and topical pre-exposure prophylaxis (PrEP) for uninfected individuals to prevent HIV-1 acquisition – are the most promising new approaches for decreasing HIV-1 spread. Observational studies among HIV-1 serodiscordant couples have associated ART initiation with a reduction in HIV-1 transmission risk of 80–92%, and a recent randomized trial demonstrated that earlier initiation of ART (that is, at CD4<sup>+</sup> T-cell counts between 350 and 550 cells/mm<sup>3</sup>), in the context of virological monitoring and adherence support, resulted in a 96% reduction in HIV-1 transmission. A number of ongoing and recently-completed clinical trials have assessed the efficacy of PrEP for HIV-1 prevention as pericoitally administered or daily-administered 1% tenofovir gel and daily oral tenofovir disoproxil

fumarate (TDF) and combination emtricitabine (FTC)/TDF. Completed studies have demonstrated HIV-1 protection efficacies ranging from 39% to 75%. However, two trials in African women have shown no HIV-1 protection with TDF and FTC/TDF PrEP; the reasons for lack of efficacy in those trials are being investigated. Adherence is likely the key to efficacy of antiretrovirals for HIV-1 prevention, both as ART and PrEP. Critical unanswered questions for successful delivery of antiretroviral-based HIV-1 prevention include how to target ART and PrEP to realize maximum population benefits, whether HIV-1-infected individuals at earlier stages of infection would accept ART to reduce their risk for transmitting HIV-1 and whether highest-risk HIV-1-negative persons would use PrEP, and whether high adherence could be sustained to achieve high effectiveness.

## Introduction

Antiretrovirals markedly increase the survival of HIV-1-infected individuals and are the cornerstone of strategies to prevent vertical HIV-1 transmission. During the past 10 years, a growing scientific and advocacy interest in antiretroviral-based strategies for prevention of sexual HIV-1 transmission has developed, and antiretroviral-based HIV-1 prevention interventions are now among the most promising strategies for greatly reducing HIV-1 spread. Antiretrovirals have the potential to be used for HIV-1 prevention as antiretroviral treatment (ART) to reduce the infectiousness of individuals with HIV-1 and oral or topical pre-exposure prophylaxis (PrEP) for uninfected individuals with repeated and ongoing HIV-1 exposure.

The past 2 years have seen significant new advances in HIV-1 prevention as a result of antiretroviral-based prevention strategies, including both ART and PrEP, and policymakers are considering implications of trials of ART and PrEP in terms of resources and programmatic implementation. This review will focus on

the rationale and evidence for ART and PrEP for HIV-1 prevention, and remaining questions and uncertainties.

## Evidence for antiretroviral treatment for HIV-1 prevention: observational studies

The primary determinant of risk of HIV-1 transmission is the concentration of HIV-1 in plasma [1,2] and genital secretions [3]. ART reduces HIV-1 plasma concentrations to undetectable levels within 6 months of initiation in the majority of individuals [4] and seminal and cervicovaginal HIV-1 concentrations are also reduced to undetectable levels in most individuals on ART [5–9]. Use of peripartum ART is responsible for the remarkable success in virtually eliminating mother-to-child HIV-1 transmission in resource-rich settings [10].

It was hypothesized that the substantial reduction in HIV-1 quantity in plasma and genital compartments in individuals on suppressive ART would translate into markedly reduced risk of HIV-1 transmission to sexual

**Table 1.** Key studies of HIV-1 prevention benefits of antiretroviral treatment

Study	Population	Patients	HIV-1 transmission outcome associated with ART use	Reference
Meta-analysis of 5 observational studies	Heterosexual HIV-1 serodiscordant couples from 11 cohorts, 1996–2009	5,021 couples (461 HIV-1 transmission events, not described whether virologically linked)	92% decrease in HIV-1 transmission risk for couples in which the HIV-1-infected partner was receiving ART (5.64 compared to 0.46 transmissions per 100 person-years)	[13]
Partners in Prevention HSV/HIV Transmission Study	Observational analysis from a prospective study of HIV-1 serodiscordant couples (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia), 2004–2008	3,381 couples (103 virologically linked HIV-1 transmissions)	92% decrease in HIV-1 transmission risk for couples in which the HIV-1-infected partner was receiving ART (2.24 compared to 0.37 transmissions per 100 person-years)	[14]
HPTN 052	Randomized trial of early versus standard (CD4 <sup>+</sup> T-cell count 350–550 versus $\leq 250$ cells/mm <sup>3</sup> , respectively) initiation of ART in HIV-1 serodiscordant couples (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, US, Zimbabwe), 2007–2010	1,763 couples (28 virologically linked HIV-1 transmissions)	96% decrease in HIV-1 transmission risk in couples assigned to receive early ART (versus standard ART initiation; 0.9 to 0.1 per 100 person-years)	[15]

ART, antiretroviral treatment.

partners [1,11,12]. A meta-analysis of data from 11 cohorts among 5,021 heterosexual HIV-1 serodiscordant couples with 1,098 person-years of follow-up found only 5 cases of HIV-1 transmission to sexual partners from HIV-1-infected individuals receiving ART, consistent with a transmission rate between 0.19 and 1.09 per 100 person-years [13] (Table 1).

Among 3,381 HIV-1 serodiscordant couples in the Partners in Prevention HSV/HIV Transmission Study, HIV-1 transmission risk was reduced by 92% (95% CI 43, 100;  $P=0.004$ ) among the 349 couples in which the HIV-1-infected partners initiated ART during follow-up (1 transmission event in 273 person-years of follow-up), compared to those who did not start ART (102 transmission events in 4,558 person-years of follow-up; Table 1) [14]. As in the meta-analysis [13], the rate of HIV-1 transmission was very low (<0.5% per year) after ART initiation. The single HIV-1 transmission event observed after ART initiation occurred <4 months after ART was started, and thus it is probable that transmission occurred prior to complete HIV-1 suppression as a result of ART. An important aspect of these observational data is that HIV-1-infected partners in the Partners in Prevention HSV/HIV Transmission Study received ART outside of research clinic settings, thus reflecting the community standard of care for ART delivery, adherence counseling and clinical monitoring. Viral load monitoring was not standard practice in the research study or in clinical settings in the study communities; retrospective

testing of a single plasma sample obtained a median of 7.3 months after ART initiation (IQR 3.4–12.1 months) demonstrated that 70% of HIV-1-infected individuals achieved virological suppression.

In the Partners in Prevention HSV/HIV Transmission Study, HIV-1 transmissions occurred across the range of CD4<sup>+</sup> T-cell count strata. HIV-1 incidence among couples where the HIV-1-infected partners had CD4<sup>+</sup> T-cell counts <200 cells/mm<sup>3</sup> was >8% per year in the absence of ART, emphasizing that the greatest priority for ART provision for both HIV-1 treatment and prevention is for HIV-1-infected individuals with lower CD4<sup>+</sup> T-cell counts. For HIV-1-infected partners who had CD4<sup>+</sup> T-cell counts >200 cells/mm<sup>3</sup>, 70% of transmissions were from those who had plasma HIV-1 RNA levels  $\geq 50,000$  copies/ml, even though they accounted for only approximately 30% of follow-up time [14]. These data suggest that high viral load (for example,  $\geq 50,000$  copies/ml) may be a useful laboratory criterion to augment CD4<sup>+</sup> T-cell counts for determining ART eligibility since it would identify individuals at higher risk of HIV-1 transmission who would benefit from earlier initiation of ART (for example, at CD4<sup>+</sup> T-cell count >350 cells/mm<sup>3</sup>, the current WHO standard is  $\leq 350$  cells/mm<sup>3</sup>).

### Definitive evidence for antiretroviral treatment for HIV-1 prevention: HPTN 052

In 2011, the observational data associating ART initiation with substantial reduction in HIV-1 risk

were confirmed by the HIV Prevention Trials Network (HPTN) 052, a randomized trial among 1,763 HIV-1 serodiscordant heterosexual couples [15]. At the time of enrolment into the trial, all HIV-1-infected partners had a CD4<sup>+</sup> T-cell count between 350 and 550 cells/mm<sup>3</sup> (thus not meeting international guidelines for ART provision). HIV-1-infected partners were randomly assigned to immediately initiate ART or wait to initiate ART until their CD4<sup>+</sup> T-cell count fell to  $\leq 250$  cells/mm<sup>3</sup>, consistent with standard practice at the time. In April 2011, the trial's independent Data and Safety Monitoring Board (DSMB) recommended a public report of the study results because HIV-1 prevention benefits of earlier ART initiation had become clearly demonstrated (that is, the statistical calculations for the study crossed a pre-specified efficacy threshold for early discontinuation of the delayed ART arm). Of 39 HIV-1 transmissions observed in the study, 28 were virologically linked within the study partnership: 27 in the delayed ART arm and only 1 in the immediate ART arm, a 96% reduction in HIV-1 risk that was highly statistically significant (relative risk 0.04, 95% CI 0.01, 0.27;  $P < 0.001$ ) [15]. The single transmission in the immediate ART arm was observed soon after ART initiation, a similar situation to what was observed in the Partners in Prevention HSV/HIV Transmission Study observational analysis. Notably, HPTN 052 conducted quarterly viral load monitoring with intensive follow-up and adherence counselling for those on ART who were not achieving viral suppression, and as a result they achieved 89% of participants on ART with viral suppression within 3 months and 97% at 24 months [15].

### Public health implications of antiretroviral treatment for HIV-1 prevention

Scientific opinion [12] and mathematical modelling [16] have stimulated great interest in the potential of ART to substantially reduce population HIV-1 incidence. Universal ART – administered through universal HIV-1 testing, linkage to care, immediate access to ART regardless of CD4<sup>+</sup> T-cell count, and optimal adherence (together called the ‘Test and Treat’ concept) – has been predicted to virtually eliminate incident HIV-1 infections, over a period of decades [16]. These mathematical models focused on hyperendemic settings with uncertain generalizability to more concentrated epidemics in more resource-rich settings. In addition, the mathematical models that indicate HIV-1 elimination is feasible require almost universal coverage, of both frequent HIV-1 testing and ART provision as well as very high ART adherence, and consequently, rates of virological suppression. Mathematical models using potentially more realistic assumptions have suggested that the impact of treatment on HIV-1 incidence could be more modest, although still

highly beneficial [17]. Uncertainties about Test and Treat include: how to address barriers in the ‘cascade’ of steps between learning one is HIV-1-infected and achieving sustained viral suppression with ART [18,19], the willingness of HIV-1-infected individuals to initiate ART at higher CD4<sup>+</sup> T-cell counts when they are asymptomatic and sustain high adherence levels and viral suppression in order to durably reduce HIV-1 transmission, availability of resources to greatly increase and sustain ART coverage, and the ultimate impact of increasing ART provision on population HIV-1 incidence, the key measure of public health prevention benefits. Evaluation of strategies to achieve high knowledge of HIV-1 serostatus, uptake of ART and retention in care is being evaluated in a feasibility study in two US cities (Bronx, NY and Washington, DC) through HPTN 065 [20]. Several large trials of the population level impact of Test and Treat strategies have been initiated in Africa, including studies in Botswana, Tanzania, South Africa and Zambia [21].

While these approaches are being evaluated, an initial focus of earlier ART provision might be HIV-1 serodiscordant couples – a smaller target population and for whom the clinical trial data [15] and mathematical modelling [22] indicate a substantial impact. WHO guidelines about testing, counselling and antiretrovirals for HIV-1 prevention in HIV-1 serodiscordant couples will be released in 2012 [23]. Considering the available evidence and mathematical modelling data, it is clear that ART has the potential to be a highly effective HIV-1 prevention strategy if implementation challenges can be met and high coverage achieved. The results of community trials and demonstration projects of ‘Test and Treat’ interventions are eagerly awaited.

### Rationale for topical and oral pre-exposure prophylaxis for HIV-1 prevention

The rationale for prevention of sexual HIV-1 acquisition with PrEP stems from efficacy of antiretrovirals for the prevention of mother-to-child transmission of HIV-1, first demonstrated with peripartum zidovudine [24]. Recent studies have shown that post-natal antiretrovirals, provided to infants who have ongoing exposure to HIV-1 through breastmilk, can substantially reduce HIV-1 risk [25]. Infant studies provide compelling analogous evidence that antiretroviral prophylaxis could be highly efficacious for preventing infection in the context of known and ongoing HIV-1 exposure [26].

Animal studies also provided evidence to suggest that antiretrovirals could be used for prevention of HIV-1 acquisition. Macaque simian HIV challenge studies [27] and more recently, humanized mouse HIV-1 challenge studies [28], have tested topical 1% tenofovir (TFV) gel, oral TDF, and oral combination

**Table 2.** Efficacy trials of topical and oral pre-exposure prophylaxis

Study (location)	Population	Participants, <i>n</i>	PrEP agent	Status	Reference
CAPRISA 004 (South Africa)	Women	889	Vaginal tenofovir gel (coitally associated use)	39% reduction in HIV-1 incidence	[37]
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, US)	Men who have sex with men and transgender women	2,499	FTC/TDF	44% reduction in HIV-1 incidence	[41]
FEM-PrEP (Kenya, South Africa, Tanzania)	Higher-risk women	1,950	FTC/TDF	Stopped for lack of efficacy in April 2011	[46,47]
Partners PrEP Study (Kenya, Uganda)	HIV-1 serodiscordant couples	4,758	TDF, FTC/TDF	67% reduction in HIV-1 incidence for TDF; 75% reduction in HIV-1 incidence for FTC/TDF	[51]
TDF2 Study (Botswana)	Heterosexual men and women, ages 18–35	1,200	FTC/TDF	62% reduction in HIV-1 incidence	[49]
VOICE/MTN 003 (South Africa, Uganda, Zimbabwe)	Women	5,021	TDF, FTC/TDF, vaginal tenofovir gel (daily use)	Oral TDF stopped for lack of efficacy in September 2011; vaginal TDF gel arm stopped in November 2011	[54,55]
Bangkok Tenofovir Study (Thailand)	Injection drug users	2,400	TDF	Ongoing	[56]
FACTS 001 (South Africa)	Women	2,600	Vaginal tenofovir gel (coitally associated use)	Initiated October 2011	[57]

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

emtricitabine (FTC)/TDF. The choices of the first candidate antiretrovirals for prevention, TDF and FTC/TDF, were based on their action early in the HIV-1 life cycle, high potency, high genital tract levels [29,30], excellent safety and tolerability, and low incidence of resistance (for example, low levels of resistance to TDF in short-term monotherapy studies) [31]. Animal model studies have tested drug dosing and delivery routes that reflect oral dosing in humans and repeat low dose mucosal virus challenges to mimic sexual exposure to HIV-1. Overall, these studies indicated high levels of protection from topical TFV gel [32] and daily oral dosing of TDF and FTC/TDF, with potentially greater protection from combination FTC/TDF than TDF alone [27,33], as well as efficacy when FTC/TDF was dosed intermittently (3 days before and 2 h after rectal viral exposure) [34]. Animal studies also are being used to identify potential new PrEP candidates, including topical maraviroc [35] and raltegravir [36].

### Human efficacy trials of topical and oral pre-exposure prophylaxis

Proof-of-concept clinical trials of the safety and efficacy of topical TFV vaginal gel, oral TDF and oral FTC/TDF as PrEP have been conducted in African women at risk of heterosexual HIV acquisition through six studies: the Center for AIDS Programme of Research in South Africa (CAPRISA 004), FEM-PrEP, Partners

PrEP, TDF2, Vaginal and Oral Interventions to Control the Epidemic study (VOICE) and FACTS is the Follow-on African Consortium for Tenofovir Studies (FACTS 001). Two of these studies enrolled African heterosexual men (Partners PrEP and TDF2). One study enrolled men who have sex with men (MSM) from the Americas, Thailand, and South Africa (Chemoprophylaxis for HIV Prevention in men [Spanish acronym: iPrEx]). One ongoing study enrolled injection drug users (Bangkok Tenofovir Study; Table 2). These studies are summarized below in chronological order of their reporting of efficacy findings.

CAPRISA 004 enrolled 889 HIV-1 uninfected women, ages 18–44 in Durban and rural KwaZulu-Natal, South Africa, who were randomized to pericoital use of 1% TFV gel or placebo, dosed by the BAT24 strategy (that is, before and after sex, not to exceed two doses in 24 h). The event-driven BAT24 strategy was developed to mimic dosing of nevirapine for prevention of mother-to-child HIV-1 transmission as it is used for peripartum prophylaxis. In CAPRISA 004, TFV gel significantly reduced the risk of HIV-1 acquisition by 39% (95% CI 6, 60;  $P=0.017$ ) [37]. Notably, HIV-1 incidence was 9.1 per 100 women-years in the placebo arm, an extraordinarily high rate. No antiretroviral resistance to TFV (that is, the K65R mutation) was detected using standard population sequencing in HIV-1 samples obtained from HIV-1 seroconverters. In subgroup analyses, efficacy was estimated to be 54% in women who

reported >80% adherence to gel use with sex acts in the prior month ( $P=0.025$ ). In a case-control analysis of cervicovaginal TFV levels among HIV-1 seroconverters and matched controls, women with levels >1,000 ng/ml had 74% lower risk of HIV-1 infection than those with <1,000 ng/ml [38], supporting evidence of an adherence-efficacy relationship. An unexpected 'bonus' of CAPRISA 004 was a 51% reduction in HSV-2 incidence among women assigned to the TFV gel arm, which is consistent with *in vitro* studies that have found that the high mucosal concentrations of tenofovir diphosphate, the active metabolite, achieved with vaginal application have direct anti-herpetic activity [39]. Concentrations of tenofovir diphosphate in vaginal tissues are approximately 100-fold higher with 1% TFV gel dosing compared to oral dosing using TDF and topical TFV gel results in little systemic absorption [40].

The iPrEx study enrolled 2,499 HIV-1-seronegative MSM and transgender women from North and South America, South Africa and Thailand in a randomized placebo-controlled trial of daily oral FTC/TDF. The majority of men were enrolled from the South American sites. The iPrEx study demonstrated that FTC/TDF reduced HIV-1 acquisition risk by 44% (95% CI 15, 63;  $P=0.005$ ). Subgroup analyses indicated higher efficacy (73%) among those with  $\geq 90\%$  adherence [41]. Importantly, plasma and intracellular drug levels from a subset of study visits demonstrated that only 8% of seroconverters and 54% non-seroconverters had detectable TDF or FTC; having detectable drug concentrations was strongly associated with substantially lower risk of acquiring HIV-1 (OR 12.9, 95% CI 1.7, 99.3). The low level of detection of drug in the non-seroconverters indicates that overall adherence in the study population was only moderate; correlates of higher adherence included age >25 years, participants from US sites and recent unprotected anal receptive sex [42]. Resistance to FTC (that is, M184I/V mutations) was detected in two participants randomized to FTC/TDF who had seronegative acute HIV-1 infection at the time of randomization. For these two individuals, FTC resistance was no longer detectable, even by ultrasensitive resistance testing, 6 months after PrEP discontinuation [43]. Although M184V resistance was rare in the breakthrough infections, retrospective drug level testing in seroconverters indicated that men became infected during periods of low exposure to FTC/TDF [44]. Some experts remain concerned about the potential for undetected archived resistance in PrEP breakthrough infections to compromise response to FTC or 3TC when such individuals initiate HAART. Safety was high with no substantial differences in the rate of serious adverse events, including laboratory events, by arm. A modest but statistically significant 1% reduction in bone mineral density was observed in the FTC/TDF

arm, compared with placebo [45]; this decline in bone mineral density is a known effect of TDF in studies of HIV-1 treatment – the effect appears to be early then stabilizes, and was not associated with increased risk of bone fracture. No risk compensation was observed based on self-reported condom use during anal sex. Thus, iPrEx indicates excellent safety and moderate efficacy in the context of moderate adherence. Rare resistance was detected (among two subjects who initiated PrEP during acute seroconversion). Uptake, adherence, risk behaviours and efficacy in the context of known efficacy of FTC/TDF PrEP is being studied among former iPrEx participants and a subset of new enrollees in an open-label extension study (iPrEx OLE).

The FEM-PrEP study enrolled 1,951 high-risk HIV-1-uninfected women from Kenya, South Africa and Tanzania into a placebo-controlled trial of daily oral FTC/TDF. The study was stopped by its Independent Data Monitoring Committee in April 2011 due to futility: an equal number of infections ( $n=28$ ) were seen in each of the two study arms [46]. Adherence was low in FEM-PrEP; 26% of non-seroconverters had consistent TDF levels detected in plasma in a retrospective case-control analysis [47]. Intensive pharmacokinetic studies indicate that differential penetration and persistence of the metabolites of TDF and FTC in cervical, vaginal and rectal tissues may make oral FTC/TDF PrEP more vulnerable to non-adherence in women than men [30,48].

The TDF2 study enrolled 1,200 heterosexual HIV-1-uninfected men and women between the ages of 18 and 40 in Botswana into a placebo-controlled trial of daily oral FTC/TDF; enrolment was terminated early due to larger-than-expected rates of loss-to-follow-up. The study reported results in July 2011: 62% efficacy (95% CI 22, 83;  $P=0.01$ ) for HIV-1 protection due to PrEP [49]. The trial was underpowered to demonstrate sex-based differences with a total of 33 seroconversions, but the point estimates were protective for both men (80%;  $P=0.03$ ) and women (49%;  $P=0.1$ ). Safety and tolerability of FTC/TDF were high. There was no evidence of behavioural risk compensation.

The Partners PrEP Study (for which we are the lead investigators) is an ongoing three-arm placebo-controlled trial of daily oral TDF and FTC/TDF among 4,758 HIV-1 serodiscordant couples from Kenya and Africa, among whom the HIV-infected partner is not eligible for ART according to national guidelines; the HIV-1-uninfected partners are randomized to receive PrEP or placebo [50]. On 10 July 2011, the study's DSMB recommended that the placebo arm be discontinued due to meeting pre-determined stopping guidelines for efficacy. The Partners PrEP Study demonstrated 67% efficacy of TDF (95% CI 44, 81;  $P<0.001$ ) and 75% efficacy of FTC/TDF (95% CI 55, 87;  $P<0.001$ )

compared to placebo; the difference between TDF and FTC/TDF was not statistically significant ( $P=0.23$ ). Both TDF and FTC/TDF significantly reduced HIV-1 risk for both men and women [51]. Adherence to study drug was very high based on clinic-based pill counts of unreturned study medication, electronic monitoring and home visits for unannounced pill counts that were done at three of the nine study sites [52], and TDF measurement in plasma, which was detectable in 82% of randomly-selected non-seroconverters [53]. Two of eight individuals who were randomized to PrEP during seronegative acute HIV-1 infection developed resistance mutations (one K65R and one M184V mutation) but no participants who acquired HIV-1 after PrEP initiation acquired mutations conferring resistance to TDF or FTC [51]. Safety of both drugs was high and no evidence of risk compensation was observed.

The VOICE trial is an ongoing five-arm study among 5,021 HIV-1-uninfected women from South Africa, Uganda, and Zimbabwe, in which daily 1% TFV gel, daily oral TDF and daily oral FTC/TDF are being evaluated for safety and effectiveness compared to respective gel/oral placebos. The DSMB for the VOICE trial recommended discontinuation of the oral TDF arm in September 2011 [54] and the daily vaginal 1% TFV gel arm in November 2011 due to inability to demonstrate efficacy [55]. The VOICE trial is continuing with the daily oral FTC/TDF arm, which will be completed by mid-2012 and will provide important safety and efficacy data for daily oral FTC/TDF among at-risk African women

Lastly, the Bangkok Tenofovir Study trial of daily oral TDF among HIV-1-uninfected injection drug users compared to placebo is fully enrolled with 2,413 participants and is anticipated to have efficacy results in 2012. A majority of the participants are enrolled in methadone replacement programmes, where they receive their study medication, essentially as directly observed PrEP [56].

### Current understanding and future directions for pre-exposure prophylaxis

Efficacy trials have demonstrated high safety and moderate to high efficacy of topical and oral PrEP among South African women (CAPRISA 004), MSM from diverse settings (iPrEx), young Botswana heterosexuals (TDF2) and East African heterosexuals with known HIV-1-infected partners (Partners PrEP). Unravelling potential behavioural and biological explanations for lack of efficacy of oral PrEP in some populations of women – FTC/TDF in FEM-PrEP and TDF in VOICE – is essential to understanding whether the lack of efficacy is primarily due to adherence to study product, types of sexual exposure and/or biological cofactors. The futility of daily 1% TFV gel in

the VOICE trial to prevent HIV-1 acquisition among African at-risk women from South Africa, Uganda and Zimbabwe was surprising, and will require analyses of adherence and biological cofactors to explain the different outcome from CAPRISA 004 with pericoital dosing. The recently-launched FACTS 001 study is a confirmatory study of the pericoital BAT24 strategy among a diverse population of South African women [57] and will provide essential data on safety and effectiveness of pericoital 1% TFV gel in order to hopefully move an effective microbicide forward to licensure and wide-scale use. TFV gel has recently been reformulated in an isoosmolar formulation for rectal application, which will be evaluated for safety and pharmacokinetics among MSM in a Microbicide Trials Network study that will be initiated in 2012.

With respect to oral TDF-based PrEP in other populations, the iPrEx trial demonstrates that daily oral FTC/TDF has moderate efficacy (44%) among young, high-risk MSM who were recruited from diverse settings in the Americas, South Africa and Thailand. Importantly, efficacy appeared to be strongly associated with adherence. The iPrEx open label extension study will determine whether knowledge of efficacy of PrEP significantly increases adherence and alters risk behaviours among MSM and thus is a viable public health strategy for MSM. The potential for intermittent dosing of oral FTC/TDF is being evaluated in HPTN 067 with a focus on pharmacokinetics, adherence and risk behaviours [58], and in a recently-initiated trial among MSM in France and Canada (IPERGAY) [59].

The Partners PrEP and TDF2 trials provide strong evidence for PrEP efficacy among African heterosexual populations, who make up the largest portion of the global epidemic [60–64]. In Partners PrEP, both TDF and FTC/TDF were highly effective in both men and women. The study enrolled HIV-1 serodiscordant couples who recognize their risk of HIV-1 [65] and achieved high adherence to daily oral PrEP [52,66]. Heterosexual HIV-1 serodiscordant couples in Africa account for a substantial proportion of new HIV-1 infections in Africa, and are an increasing focus of HIV-1 prevention efforts [23,67]. Antiretroviral-based prevention for HIV-1 serodiscordant couples could involve a staged approach to ART for the HIV-1-infected partner and PrEP for the HIV-1-uninfected partner, in which PrEP is targeted to the highest-risk couples before the HIV-1-infected partner is eligible for ART by national guidelines and elects to initiate ART, and during the first 6 months after their partner initiates ART and achieves viral suppression [68]. This staged strategy will be evaluated in open-label demonstration projects among Kenyan and Ugandan HIV-1-serodiscordant couples, an important next step after the HPTN 052 and Partners PrEP efficacy results, and which will provide data in the next

**Figure 1.** Treatment as prevention and tenofovir-based topical and oral pre-exposure prophylaxis: HIV prevention efficacy from completed clinical trials

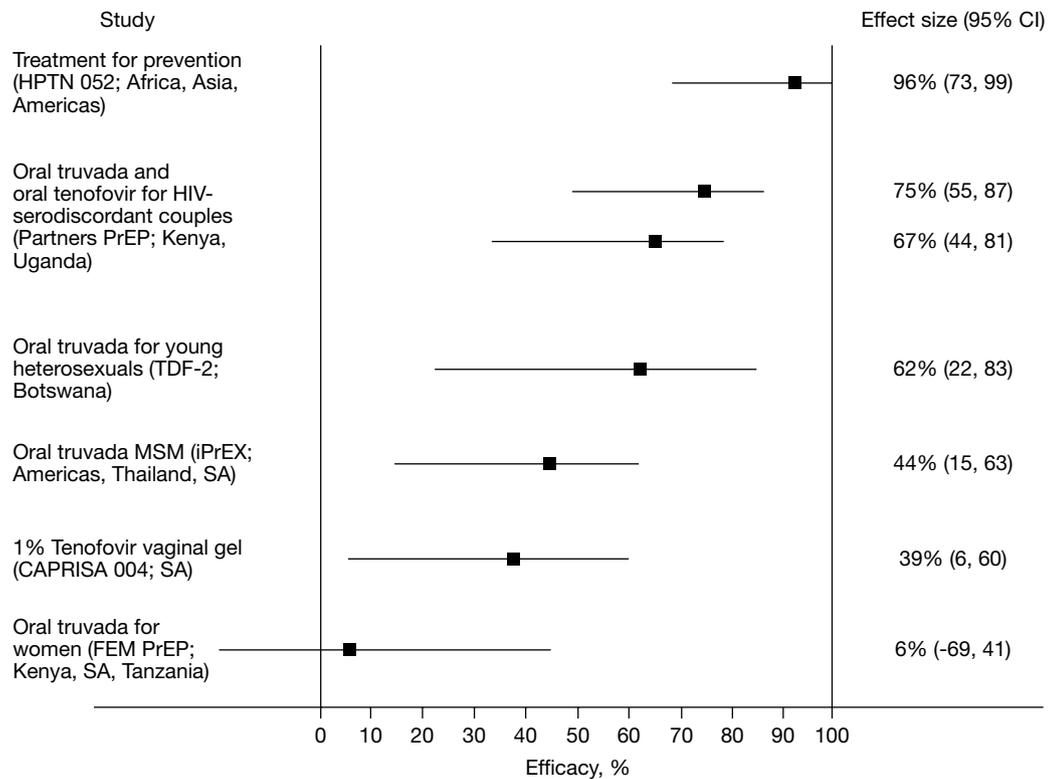


Figure does not include oral tenofovir disoproxil fumarate (TDF) data from VOICE, as data have not been released. HPTN, HIV Prevention Trials Network; MSM, men who have sex with men; SA, South Africa.

few years for implementation of antiretroviral-based HIV-1 prevention for HIV-1-serodiscordant couples.

Additional analyses – particularly examining adherence – in the FEM-PrEP and VOICE studies will be necessary to understand fully what those trials mean for PrEP use in high-risk women in some African settings. Partners PrEP and TDF2 have shown that PrEP is effective in women, but high-risk populations of women, for behavioural (for example, adherence and sexual risk) or biological (for example, presence of risk factors that heighten HIV-1 risk) reasons, may not have received benefit from PrEP in FEM-PrEP and VOICE.

While awaiting findings from recently-completed and ongoing trials of oral and topical tenofovir-based PrEP in women and injection drug users, it is important to recognize the importance of these initial trials to demonstrating proof-of-concept of antiretroviral-based primary HIV-1 prevention. Much more needs to be understood about targeting of these strategies to those at highest risk in order to be a cost-effective intervention [69,70], evaluating programme delivery

models to reduce the risk of PrEP use in acute HIV-1 infection where the risk of resistance appears to be greatest [41,71], motivating and monitoring adherence to PrEP, and messaging about PrEP as part of a combined risk reduction strategy, given its partial efficacy for HIV-1 prevention (Table 2 and Figure 1). Longer-term safety, adherence and efficacy needs to be assessed in the context of less frequent visits and briefer counselling than was provided in the intensive proof-of-concept trials.

Some individuals at risk of HIV-1 would prefer to use PrEP intermittently, which requires greater understanding of the pharmacokinetics and adherence to intermittent dosing of tenofovir-based PrEP, as will be assessed in HPTN 067. While macaque studies demonstrate biological feasibility of intermittent oral PrEP dosing, human studies are needed to determine the extent to which individuals at high risk of HIV-1 are able to anticipate sexual activity and achieve sufficient pre-exposure and post-exposure dosing to confer protection.

The PrEP field is also evaluating new candidate products, including non-nucleoside reverse transcriptase inhibitors (dapivirine and rilpivirine) and maraviroc, as well as sustained release delivery systems to provide more options with less dependence on coitally dependent or daily dosing. Dapivirine has excellent safety and sustained dispersion in a vaginal ring formulation developed by the International Partnership for Microbicides [72], and will be studied for efficacy in collaboration with the US Microbicides Trials Network (MTN 020, ASPIRE trial), beginning in 2012. Oral maraviroc will be evaluated in a comparative safety and tolerability study (HPTN 069). Dapivirine and maraviroc are being coformulated in a vaginal ring formulation. Rilpivirine, a non-nucleoside reverse transcriptase inhibitor recently-licensed for treatment, has been formulated into a parenteral formulation for prolonged plasma exposure, and is being evaluated for pharmacokinetics and dose ranging in early clinical trials. Tenofovir is being developed for a vaginal ring formulation and is currently in preclinical evaluation. Other candidate compounds and delivery systems (for example, a dissolvable film) are in preclinical stages of evaluation.

## Summary

HPTN 052 provides definitive evidence that ART has substantial prevention benefits. The challenge now will be identification of resources to increase ART coverage for the approximate 54% of HIV-1-infected individuals globally in 2010, who were eligible for ART under current WHO guidelines [73]. ART for HIV-1-infected partners with CD4<sup>+</sup> T-cell count >350 cells/mm<sup>3</sup> who are in a known serodiscordant partnership has been recommended in WHO guidelines [23]. Further expansion of earlier ART to HIV-infected individuals without regard to their partner's HIV-1 serostatus who are at risk of transmission based on other behavioural criteria is being considered and debated [74]. The challenges will not only be resources, but scale-up of HIV-1 testing to achieve high coverage of knowledge of HIV-1 serostatus, effectiveness of linkages to HIV-1 care after learning of HIV-1 infection, the willingness of HIV-1-infected individuals to initiate ART at higher CD4<sup>+</sup> T-cell counts, and the proportion of those who initiate ART to achieve and sustain viral suppression.

Proof-of-concept has been demonstrated for TDF-based topical (pericoital administration) and daily oral PrEP for primary prevention. Completion of the remaining trials and analyses of the VOICE and FEM-PrEP trials are needed to have a more complete understanding of effectiveness in different populations, particularly the relationship between adherence and efficacy. Demonstration projects in populations where PrEP has been found to be effective are needed to evaluate targeted implementation and cost-effectiveness of PrEP. Effective

HIV-1 prevention requires choices of primary prevention strategies such as PrEP, and scale-up of secondary prevention including ART for HIV-infected individuals. While the public health impact of PrEP is anticipated to be greater as products and delivery systems with sustained coverage are identified, those studies will take several years to complete. In the meantime, targeted provision of daily oral TDF-based PrEP to populations at high-risk of HIV-1 acquisition should be evaluated for inclusion as part of combination HIV-1 prevention programmes, which should also include ART for HIV-1-infected individuals as the cornerstone.

Implementation of both earlier ART for HIV-1 prevention as well as clinical benefits and PrEP will face significant logistical, cost and commitment hurdles. However, there is now excellent scientific evidence that these strategies reduce HIV-1 risk to a significant degree and thus, could alter the course of the HIV-1 epidemic.

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## Disclosure statement

The authors declare no competing interests.

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