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ORIGINAL PAPER

Pre-Exposure Prophylaxis and the Promise of Combination Prevention Approaches

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Abstract Pre-exposure prophylaxis (PrEP) for HIV prevention is a promising experimental approach currently being tested globally. A number of PrEP trials are evaluating the safety and effectiveness of PrEP in men who have sex with men (MSM) and other populations at risk for HIV, and results will be available from this first generation of efficacy trials over the next few years. Here we review the rationale for orally-administered antiretrovirals for prevention, and outline issues the first generation trials will address as well as questions that may be addressed in future studies. We also describe the rationale for combination prevention approaches that may combine PrEP with other prevention modalities as part of a larger prevention package.

Keywords Pre-exposure prophylaxis · Clinical trials · HIV prevention · Combination prevention

Introduction

"Can a pill a day prevent HIV?" That is the tagline of recruitment advertisements for an HIV prevention trial to test whether a combination pill (tenofovir/emtricitabine or Truvada®) can reduce the number of HIV infections when taken daily by men who have sex with men (MSM). This approach, also known as pre-exposure prophylaxis (PrEP), is being evaluated in a number of studies in different populations worldwide, using either a daily tenofovir or Truvada® pill. Early data from PrEP trials were presented at the International AIDS Society conference in Vienna in July 2010 [1–3]; additional results are likely to be presented and/or published prior to this article appearing in print. Tenofovir gel is also being evaluated as "topical PrEP" (also known as microbicides) vaginally and rectally, and is more fully described in the article by McGowan in this issue of *AIDS and Behavior*.

In this article, we will review the rationale for using orally-administered antiretrovirals for prevention in HIV negative persons, both as post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP). We will outline the issues the first generation of trials are designed to address as well as questions that must be addressed by future studies. Because pills alone will never completely control the AIDS epidemic, we will also discuss the rationale for combination prevention approaches that may combine PrEP (if proven efficacious) with other prevention strategies.

Rationale for HIV Prophylaxis Using Antiretroviral Agents

A number of infectious diseases can be prevented by administering antimicrobials to persons at high-risk of acquiring the disease prior to and during periods of exposure. For example, persons traveling in regions of the world with high rates of malaria take anti-malarial agents to prevent infection [4]. Antiretroviral agents have greatly reduced HIV transmission to newborns when provided to HIV-positive mothers at the time of delivery [5].

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The first demonstration that antiretrovirals could be used to prevent HIV infection came from studies in the early 1990's of zidovudine prophylaxis in mice [6] and non-human primates [7]. These and later studies demonstrated that antiretrovirals were most efficacious if given prior to or within hours after HIV or SIV challenge, and continued for 4 weeks. Tsai [8] later demonstrated the improved efficacy of PMPA (tenofovir) over zidovudine in protecting adult macaques against intravenous SIV challenge. More recent studies have demonstrated the efficacy of tenofovir or Truvada® in preventing infections when animals are challenged rectally with SIV [9].

These studies, in fact, served as a proof of principle for post-exposure prophylaxis (PEP), that is, administering antiretroviral agents within hours after an HIV exposure, and continuing treatment for 4 weeks. Although no randomized controlled trial of PEP has been conducted in humans, an observational case–control study in health care workers with occupational exposures demonstrated a significantly lower rate of HIV infection among those who took AZT compared to those who did not [10], leading to the US Centers for Disease Control and Prevention's recommendations for PEP for occupational exposures [11], and eventually for high-risk non-occupational exposures [12].

Animal data suggest that for PEP to be effective, persons at risk would have to recognize they had been potentially exposed to HIV and initiate treatment within hours of exposure, making PEP an unlikely strategy for reducing HIV incidence in populations with repeated high-risk exposures. In fact, a number of PEP failures occurred in MSM who were given antiretrovirals to keep at home, but who did not initiate PEP because they did not recognize exposures as high risk [13]. A prospective study of high-risk uninfected MSM from six US cities found that only a small fraction had single exposures to HIV prior to their infection; almost all had repeated exposures, and few recognized the frequency of exposures [14]. This would suggest that, to be effective, antiretroviral agents might need to be administered throughout periods of risk, the rationale behind PrEP.

PrEP Trial Overview

The first generation of PrEP trials are projected to enroll a diverse population of more than 20,000 men and women in Africa, the Americas, and Asia (Table 1). Three PrEP studies to date have focused on MSM populations: a safety study of daily oral tenofovir in US MSM; an efficacy study of oral daily Truvada® in MSM in Peru, Ecuador, Brazil, the US, South Africa, and Thailand; and a study of PrEP safety, feasibility, and acceptability in young MSM. Other PrEP trials are exploring the safety and efficacy of tenofovir-based regimens in injection drug users (IDU), heterosexual men and women, or heterosexual couples. A website with frequently updated information about clinical PrEP trials is hosted by the AIDS Vaccine Advocacy Coalition: http://www.prepwatch.org.

Tenofovir-based regimens were chosen on the strength of pre-clinical trials, as well as the excellent safety, tolerability, and resistance profiles of these regimens when used for HIV treatment. Each of these trials will provide substantial tolerability and safety data in these diverse populations. Some trials are conducting sub-studies to assess specific safety concerns, such as additional laboratory assays to evaluate potential renal toxicity, or dual energy X-ray absorptiometry (DEXA) to evaluate the effect of tenofovir-based regimens on bone mineral density and body composition.

All studies will measure pill-taking practices through participant self-report; many studies will augment these studies through objective measures (e.g., counting returned pills, microchips that record opening of pill bottles, drug levels in plasma, blood cells, and/or hair). There is, as yet, no "gold standard" for measuring true pill-taking practices, but these studies will evaluate the correlation between various measures of pill adherence, and ultimately, whether any of these measures is highly correlated with PrEP efficacy.

All studies are also assessing sexual and drug-use practices during the course of the trial. Concern has been raised that persons may increase their risk practices if they have access to effective prevention strategies; this change in risk behavior may be due to a reduction in self-imposed limits to avoid risk (behavioral disinhibition) or decreasing perception of risk (risk compensation) with the availability of the new prevention tool [15, 16]. The CDC-sponsored US trial of oral daily tenofovir in MSM will directly assess the potential for a change in sexual risk practices through its unique study design: half of the participants are randomized to take a daily pill (tenofovir or placebo) upon enrollment, while the other half are randomly assigned to wait 9 months before starting their daily study pill (Fig. 1). This allows a direct comparison of risk practices while men are or are not taking a daily pill, and may provide an early indication if there is likely to be substantial risk compensation. However, because participants in this trial know the efficacy of PrEP is not yet proven, and that they may be receiving placebo, this measure may under-estimate risk compensation that could occur if PrEP is found to be efficacious, and if persons are to take PrEP outside the context of a placebo-controlled trial.

Most of these studies are also powered to evaluate PrEP efficacy. Most are evaluating a single daily oral regimen, although the Partners in Prevention trial will evaluate both daily oral tenofovir versus Truvada®, and the VOICE trial

Table 1 Current oral PrEP trials (August 2010)

Study name	Population and locations tested	Study sponsor; funder	Regimen	Major questions addressed	Study timelines
US extended safety trial	400 MSM in US	CDC	Daily oral TDF	Biological and behavioral safety of daily oral TDF	Enrollment began: Q1 2005 Fully enrolled: Q3 2007 Results presented: Q3 2010
Bangkok tenofovir study	2,400 injection drug users in Thailand	CDC	Daily oral TDF	Safety and efficacy of daily oral TDF in IDU (over 80% DOT)	Enrollment began: Q2 2005 Fully enrolled: Q2 2010 Results expected: 2011
TDF 2	1,200 heterosexual men and women in Botswana	CDC	Daily oral FTC/TDF	Safety and adherence in young heterosexual men and women in Africa	Enrollment began: Q2 2007 Enrollment stopped early Results expected: 2011
iPrEx	2,499 MSM in Peru, Ecuador, Brazil, US, Thailand, and South America	NIH; BMGF	Daily oral FTC/TDF	Safety and efficacy of daily oral Truvada in MSM globally	Enrollment began: Q3 2007 Fully enrolled: Q4 2009 Results published: Q4 2010
Partners PrEP	4,700 serodiscordant heterosexual couples in Kenya, Uganda	BMGF	Daily oral TDF; Daily oral FTC/TDF	Safety and efficacy of daily oral tenofovir and Truvada in serodiscordant couples in Africa	Enrollment began: Q3 2008 Enrolling Results expected: 2012
VOICE	5,000 heterosexual women in Malawi, South Africa, Uganda, Zambia, Zimbabwe	MTN, NIH	Daily oral TDF; Daily oral FTC/TDF; Daily topical tenofovir gel	Safety and efficacy of daily oral tenofovir, daily oral Truvada, and daily topical tenofovir in African women	Enrollment began: Q3 2009 Enrolling Results expected: 2013
FEM-PrEP	3,900 heterosexual women in Kenya, Malawi, South Africa, Tanzania, Zambia	FHI, USAID, BMGF	Daily oral FTC/TDF	Safety and efficacy of daily oral Truvada in African women	Enrollment began: Q2 2009 Enrolling Results expected: 2013
IAVI E001 and E002	150 serodiscordant couples and men and women in Kenya, Uganda	IAVI	Daily oral FTC/TDF; Intermittent oral FTC/TDF (twice weekly + post-coital dosing)	Safety and adherence of daily versus intermittent FTC/TDF	Enrollment began: Q2 2009 Fully enrolled Results presented: Q3 2010
PrEP in YMSM	99 young MSM in the US	ATN, NICHD	Daily oral FTC/TDF	Safety, acceptability, and feasibility in young US MSM	Enrollment began: Q2 2009 Enrolling Results expected: 2011

CDC Centers for Disease Control and Prevention; *NIH* National Institutes of Health; *BMGF* Bill and Melinda Gates Foundation; *FHI* Family Health International; *USAID* United States Agency for International Development; *IAVI* International AIDS Vaccine Initiative; *MTN* Microbicides Trial Network; *ATN* Adolescent Trial Network; *NICHD* National Institute of Child Health and Human Development

Table adapted from AVAC's PrEP Trials Table (http://www.avac.org/prep)

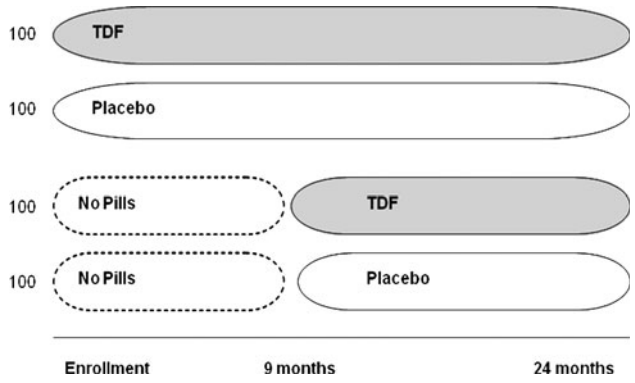

Fig. 1 Study design of US CDC tenofovir (TDF) study

will evaluate daily tenofovir, Truvada®, and daily vaginal tenofovir. While neither of these multi-arm trials is powered for a direct head-to-head comparison of regimens, both will provide comparative efficacy data within the same trial. These studies will also provide preliminary data on impact on HIV viral load setpoint, CD4 cell counts, and patterns of HIV resistance among seroconverters who become infected while taking PrEP.

Lessons Learned and Future Directions

Adherence is Critical

Optimizing adherence and its measurement in prevention clinical trials is critical for trial outcomes and interpretation. The CAPRISA 004 study of tenofovir vaginal gel provided an important proof of concept that antiretroviral agents can prevent HIV acquisition [3]. However, the trial also demonstrated the importance of adherence in ultimate PrEP effectiveness: self-reported high adherers (>80% adherence as measured by returned gel applicators) had a significant protective effect (54% effectiveness, 95% confidence interval (CI) 4–80%), while low adherers (<50% adherence) had no significant protection (28% effectiveness, 95% CI 40–64%). Data from the iPrEx trial of oral daily Truvada® in MSM is not yet available at the time of this writing. However, analyses are planned to evaluate the effect of adherence (as measured both by self-report and drug levels) on PrEP efficacy.

One challenge to interpreting efficacy results is the veracity of self-reported measures, where over-reporting may commonly occur. In the Carraguard vaginal microbicide trial, for instance, adherence to prescribed microbicide use was 96% via self-report but only 42% on the basis of applicator testing [17]. Data from a sub-study of the US-based MSM safety trial found relatively poor correlation between various adherence and drug exposure measures [18]. Many factors may be responsible for these discrepancies, including misunderstanding of study questions, memory lapses, social desirability bias, or differences in drug absorption, metabolism, or penetration into various tissues. Adherence and drug exposure measures will be most useful if they can reproducibly define patterns or thresholds of pill-taking required for maximum effectiveness, and point to mechanisms by which effectiveness may be impaired. Strategies to promote pill use in PrEP trials and to facilitate accurate reporting of product use are currently being explored [19].

Only limited data to date have been presented on adherence patterns in oral PrEP trials. Preliminary analysis from a comparison of daily versus fixed plus post-coital dosing in Kenya and Uganda suggested that adherence to daily and fixed-dose regimens were relatively high and better than post-coital dosing, although accurate measurement of post-coital pill use may have been an issue [2]. It is not yet known what schedule of PrEP dosing will be most effective, nor what level of adherence will be required for maximum tolerability and efficacy.

Importance of Community Engagement in All Stages of Research

Early planned PrEP trials (efficacy trials in Cambodia, Cameroon, Malawi, and three West African sites) were not launched or were stopped prematurely because of ethical, political, and logistical issues raised by community members, advocates, government officials, and clinical trial sponsors [20]. Difficult as these situations were for all parties involved, the resulting discussions that arose as a result of these challenges strengthened the next generation of trials, which included full involvement of community members, support of government officials, and strong oversight of clinical study operations. Community consultation must start early and involve multiple community groups, which may have distinct perspectives and interests. These engagement efforts should promote communication between researchers and community as well as among different community groups through transparent discussions [21]. UNAIDS has recently issued a revised version of good participatory practice (GPP) for biomedical HIV prevention trials [22]; this document highlights the importance of stakeholder engagement at each stage of the research life-cycle.

Attention to Trial Planning and Conduct is Paramount

In addition to the importance of community engagement, the successful conduct of PrEP research requires great attention to the mechanics of clinical trial implementation. PrEP trials are highly complex, and successful conduct of PrEP trials depends on talented investigators with access to

appropriate populations to achieve rapid accrual rates, adequate seroincidence in the context of best prevention strategies, and adherence to protocol requirements. PrEP clinical trials have faced numerous challenges on these fronts. For example, the US PrEP trial among MSM experienced slower than projected enrollment; important lessons learned included the importance of centrally coordinated recruitment strategies and campaigns, and the need for streamlined regulatory approvals and support for innovative strategies, including use of the Internet [23]. Lower seroincidence was observed in both the West African PrEP study [24] and CDC Botswana trial [25], but may have been due to overall secular trends in the community, inaccurate pre-trial estimates of HIV incidence, and intensive prevention services provided in the trial. Adherence to protocol requirements is also critical. Missed visits and pregnancy were primary reasons for time off study drug in the West African PrEP study. Low retention in the CDC Botswana PrEP study contributed to the premature closure of that trial. Ideally, plans to achieve rapid enrollment, adequate HIV seroincidence, and excellent retention rates in trials should begin prior to study launch, and adequate resources should be in place to address difficulties.

Many Questions Will Remain After the First Round of PrEP Studies

Even if all of the first and second generation PrEP studies are conducted with excellent adherence to study procedures, many questions will remain after results are available (Table 2). Data to date suggest that oral tenofovir is relatively well-tolerated in HIV-negative individuals, with no substantial safety concerns after up to 12 months of use in women in West Africa [24] and up to 24 months in MSM in the US [1]. However, only preliminary safety analyses were presented on the US MSM safety trial; additional analyses, including studies of the effect of daily tenofovir or Truvada® on bone mineral density have not yet been completed. In addition, safety data have not yet been reported for other populations, including IDU and youth, and are not collected comprehensively in pregnant or lactating women, or in persons with underlying medical conditions. Also, the long-term safety of ongoing use of antiretrovirals for prevention is unknown.

All PrEP efficacy studies will measure drug resistance in breakthrough infections. However, numbers of infections on PrEP may be small, and pooling data across PrEP studies will help identify resistance issues. All current studies focus on tenofovir-based regimens; there is interest in developing other antiretroviral agents for PrEP to improve on the safety and/or efficacy profile, or to reduce the possibility of drug resistance.

Some of the most substantive questions will need to be addressed if PrEP is found to be efficacious in clinical trials. Modeling exercises suggest that PrEP could substantially reduce new infections at a population level, but that efficacy could suffer if risk practices also increase [26, 27]. If PrEP is found to be efficacious, additional studies to measure the effect of knowledge of PrEP efficacy on risk behavior and adherence will be needed. PrEP impact may be highest if delivered to those at highest risk of acquiring HIV. Several studies have surveyed MSM about their interest in taking PrEP if found to be efficacious, and these suggest that men with substantial risk may be willing to take PrEP [28–30]. However, whether and how these men might use PrEP is not yet known. Substantial work is required to determine how best to deliver PrEP to various populations in various settings [31]. PrEP delivery will require coordination of different PrEP delivery components, including outreach, screening, drug prescribing and delivery, HIV and additional safety testing, and interventions to sustain pill use and behavioral risk reduction over the long term [32]. In addition to consideration of various political, legal, and cultural issues, questions remain about the frequency and intensity of clinical monitoring and HIV testing, how best to identify and engage high-risk populations, methods of reimbursement, and the types of clinical or community-based facilities that may be best equipped to deliver PrEP in various settings.

Combination Prevention Strategies

No infectious disease has been eliminated through antimicrobials alone; control of the HIV epidemic is most likely to come through a combination of biomedical and behavioral interventions [33]. For example, the 50% reduction in mortality from coronary heart disease from 1980 to 2000 in the US was achieved through a relatively equal contribution of modification of risk factors (e.g., decreasing prevalence of smoking) and biomedical interventions (e.g., interventional and pharmacologic therapies) [34]. Understanding the factors leading to epidemic spread, as reported in Anderson and May's classic article [35], suggests that combination interventions that target different mechanisms of an epidemic may be synergistic at a population level. For example, Hallett modeled the impact of combining widespread male circumcision with a behavior change program in South Africa [36]. In this model, widespread male circumcision (90% coverage) alone would lead to an approximate 1/3 reduction in HIV incidence at a population level; a behavior change program with a 30% reduction in partner change rate and 30% increase in condom use would lead to an approximate 2/3 reduction in HIV incidence rates. However, if male

Table 2 Data available from current PrEP trials, and areas for future studies

	Data provided by current trials	Gaps to be addressed in future trials
Biological safety (frequency of adverse events, including renal, hepatic, bone, and metabolic toxicities)	Clinical safety of daily oral TDF in MSM, IDU	Safety of longer term use (>several years) in all populations
	Safety of FTC/TDF in MSM, heterosexual men and women and serodiscordant couples in Africa	Safety of use in pregnancy or breastfeeding
	Safety of intermittent FTC/TDF in serodiscordant couples and men and women in Africa	Safety in persons with chronic disease (renal, hepatic)
	Safety of daily vaginal tenofovir gel in African women	Optimal frequency of safety monitoring
		Safety of other medications for PrEP
		Safety of topical tenofovir gel for rectal use
Efficacy	Efficacy of daily oral FTC/TDF in MSM, heterosexual men and women in Africa, and serodiscordant couples	Comparative efficacy of intermittent PrEP versus daily PrEP
	Efficacy of daily oral TDF in IDU	Efficacy of other medications for PrEP and other routes of administration
	Efficacy of daily vaginal tenofovir gel	Mechanisms for differences (if found) in efficacy results between different trials
	Efficacy for different routes of exposure, including anal/penile (MSM), penile/vaginal (heterosexual men and women), and parenteral (IDU)	
	Effect on HIV viral load set point and CD4 among seroconverters	
	Validation of non-human primate models of PrEP efficacy	
Adherence	Rates of pill or gel use based on multiple adherence measures within a clinical trial	Pill or gel use rates when efficacy of PrEP is known and PrEP is taken outside of a clinical trial context
	Correlation between different adherence and drug exposure measures	Reproducible, easily obtained measures of drug exposure that can be used in clinical practice
Behavior	Effect of pill-taking on risk behavior in multiple populations participating in double-blind, placebo-controlled studies	Effect of pill-taking on risk behavior when efficacy is known and PrEP is provided outside of a clinical trial context
Resistance	Preliminary data on resistance patterns seen in seroconverters	Rates of drug resistance with expanded PrEP use in the community
		Optimal frequency of HIV testing to minimize resistance but increase feasibility of PrEP delivery

circumcision were combined with a behavior change program, HIV incidence would be virtually eliminated.

Similar to topically-applied PrEP, which was recently shown to be 39% effective in reducing HIV infections in African women [3], oral PrEP is unlikely to be 100% effective. PrEP would therefore need to be combined with other prevention interventions to have the biggest impact. Other articles in this issue of *AIDS and Behavior* review other types of interventions that may be useful for controlling the HIV epidemic in MSM, and if efficacious, may be combined with PrEP to increase the protective effect. In particular, it will be important to test interventions that could be coupled with PrEP to minimize risk compensation and maximize adherence in the setting of known efficacy and implementation outside of clinical trials. Other behavioral interventions, treatment of substance abuse, rectal microbicides, increased HIV testing and disclosure, and programs to promote the sexual health and overall well-being of MSM may all play an important role in control of the HIV epidemic in MSM. Combination prevention interventions will need to be feasible to deliver and attractive to diverse MSM populations. The Prevention Umbrella for MSM in the Americas (PUMA) is an R01-funded planning project to evaluate how best to combine and deliver a package of interventions to have the biggest impact on driving down HIV infection rates in MSM.

The next few years will tell us whether PrEP can be efficacious and deliverable in diverse populations of MSM worldwide. Future efforts will focus on maximizing the effectiveness and cost-effectiveness of PrEP, and

combining PrEP with behavioral and biomedical interventions to drive down HIV incidence in MSM and other populations at risk for HIV.

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