Antiretroviral Prophylaxis for Sexual and Injection Drug Use Acquisition of HIV

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Abstract: During the past few years, much has been learned about pre-exposure prophylaxis (PrEP) of HIV from studies conducted in the U.S. and elsewhere. A review and summary was conducted of articles and reports published through August 2012 on the safety and efficacy of PrEP in humans; U.S.-based studies assessing PrEP knowledge, attitudes, and use among at-risk populations and healthcare providers; and models of the cost effectiveness of PrEP. PrEP is generally safe and effective and may be cost effective in a targeted population. Awareness and interest in PrEP are increasing. PrEP is an important new addition to HIV prevention services, but continued study is warranted.
(Am J Prev Med 2013;44(1S2):S63–S69)

Introduction

The recent FDA determination that there are sufficient safety and efficacy data to approve the use of Truvada® to prevent sexual acquisition of HIV infection and the issuance of interim guidance by CDC for preexposure prophylaxis (PrEP) in men who have sex with men (MSM)[1] and heterosexually active adults[2] at very high risk of HIV acquisition have increased interest in understanding the data on which they relied and other data important to considering the introduction of PrEP as an HIV prevention method in the U.S.[3]

Clinical Trials Evaluating the Safety and Efficacy of Daily Oral Antiretroviral Pre-Exposure Prophylaxis

The drugs evaluated in pre-exposure prophylaxis (PrEP) clinical trials are the reverse transcriptase inhibitors tenofovir disoproxil fumarate (TDF) alone or emtricitabine (FTC) in combination with TDF (TDF–FTC; marketed under the brand name Truvada). These drugs were chosen because of high potency, low likelihood of inducing resistance, little toxicity, daily dosing, and high concentrations in genital fluids. All participants in the PrEP trials were afforded a comprehensive package of HIV prevention services (e.g., counseling, condoms, treatment for sexually transmitted infections). The reductions in risk of HIV acquisition, where found, represent protection beyond that found with a comprehensive prevention package alone. Table 1 provides an overview of PrEP clinical trials.

The West African PrEP Safety Trial. This trial was conducted in Ghana, Cameroon, and Nigeria among 936 HIV-uninfected women randomly assigned to TDF or placebo.[4] No differences in clinical and laboratory safety endpoints were noted between the two groups over 476 person-years of follow-up. The point estimate for protection was 65% (incidence 0.86 vs 2.48/100 person-years), but had a wide CI (relative risk=0.35, 95% CI=0.03, 1.93, p=0.24). Among 363 participants on TDF, none had a Grade 3 or greater alanine aminotransferase (ALT) or aspartate aminotransferase (AST) liver function test. Among 368 participants on placebo, two had Grade 3 or greater ALT, and three had a Grade 3 or greater AST. No difference was found between those on TDF and those not on TDF in the frequency of Grades 1 or 2 hepatic enzyme increases. Among 56 participants positive for hepatitis B surface antigen (HBsAg), 23 were assigned to TDF and 33 to placebo[4]; no serious increases or difference in mean or median values of ALT and AST were seen in those on active drug and those on placebo.

The U.S. PrEP Safety Trial in MSM. This trial was a Phase II trial of oral daily TDF among 400 HIV-1 seronegative MSM.[11] Investigators found no difference in the frequency of serious adverse events between the TDF and placebo arms (27 vs 11 events, p=0.56). The rate of creatinine and phosphate laboratory abnormalities was similar between the study arms. The study was not designed or powered to assess efficacy.

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0749-3797/$36.00
http://dx.doi.org/10.1016/j.amepre.2012.09.045

Table 1. Studies of safety and efficacy of daily oral HIV PrEP, 2004–2011

Study	Locations	Study drug(s)	HIV risk group	PrEP risk reduction, % (95% CI)
West African PrEP Safety Trial[4]	Ghana, Cameroon, Nigeria	Oral daily TDF	High-risk heterosexual women	65 (NS) [RR=0.35 (0.03, 1.93) p=0.24]
iPrEx[5]	Peru, Ecuador, South Africa, Brazil, Thailand, U.S.	Oral daily TDF–FTC	MSM and transgender	44 (15, 63)
Partners PrEP[6]	Kenya, Uganda	Oral daily TDF and TDF–FTC	HIV-discordant heterosexual couples	TDF: 67 (44, 81) TDF–FTC: 75 (55, 87)
TDF2[7]	Botswana	Oral daily TDF–FTC	High-risk heterosexual men and women	63 (22, 83)
FEM-PrEP[8]	Kenya, Malawi	Oral daily TDF–FTC	High-risk heterosexual women	Stopped for futility
VOICE[9]	South Africa, Uganda, Zimbabwe	Oral daily TDF, TDF–FTC; vaginal tenofovir gel	High-risk heterosexual women	Stopped TDF oral and tenofovir vaginal gel arms for futility
Bangkok Tenofovir Study[10]	Thailand	Oral daily TDF	Injection drug users	Fully enrolled; results pending

FTC, emtricitabine; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; RR, relative risk; TDF, tenofovir disoproxil fumarate

iPrEx. This study was a Phase III trial in which 2499 men (including 29 transgender women) who have sex with men were assigned randomly to receive daily oral TDF–FTC or placebo and, after 3324 person-years of follow-up, there was a 44% (95% CI=15%, 63%) reduction in risk among PrEP recipients.[5] In a case–control substudy among subjects with detectable drug levels versus those without, the relative reduction in HIV acquisition risk was 92% (95% CI=40%, 99%).

In iPrEx, side effects were typically minor, self-limited, and occurred early after initiation of PrEP. Some minor gastrointestinal adverse events (e.g., nausea) were more common in those in the active arm, but resolved after the first month taking the drug. Two percent of men taking TDF–FTC and 1% of men taking placebo had creatinine elevations at least 1.1 times the upper limit of normal. Of those, 88% were not confirmed on repeat testing, with elevations in more than one consecutive test in five (1%) of the TDF–FTC recipients and none of the placebo recipients. By protocol, ten participants (seven on TDF–FTC and three on placebo) stopped drug due to creatinine elevations, but nine restarted without recurrence. All participants who had elevations that led to drug discontinuation had resolution of creatinine levels to normal.

Partners PrEP. This study was a Phase III trial that enrolled 4758 HIV-discordant heterosexual couples in Kenya and Uganda. Uninfected partners were randomized to receive daily oral TDF, TDF–FTC, or placebo.[6] The investigators reported 67% (95% CI=44%, 81%) and 75% (95% CI=55%, 87%) reduction in HIV transmission risk in the TDF and TDF–FTC groups, respectively, compared to placebo. Both drugs were safe and well tolerated, except for early mild gastrointestinal side effects.

TDF2. This study was a Phase IIb trial performed in 1219 heterosexual men (55%) and women (45%) in Botswana and found that TDF–FTC afforded a 63% (95% CI=22%, 83%) reduction in risk of acquiring HIV infection when compared to placebo.[7] Protection was greater (78%) among participants who had been dispensed pills within the 30 days prior to their last HIV test. No safety concerns were noted except for some increased risk of nausea, vomiting, and dizziness.

FEM-PrEP. This study was a Phase III trial of daily oral TDF–FTC versus placebo that planned to enroll 3900 high-risk women, aged 18–35 years, in Africa.[8] In April 2011, after 56 incident infections had occurred, the study was stopped because of futility: 28 infections occurred in each arm. No safety concerns were noted but poor medication adherence may have played a major role in the lack of efficacy.

VOICE. The VOICE study enrolled 5029 HIV-negative women in a Phase III trial comparing TDF vaginal gel, daily oral TDF, and daily oral TDF–FTC to their respective placebos.[9] In 2011, the oral TDF and the vaginal tenofovir gel arms of the study were stopped because of lack of efficacy. There were no safety concerns with either oral drug or the vaginal gel, and evaluation of efficacy in the daily oral TDF–FTC arm is continuing.

Table 2. Measures of efficacy by medication adherence in HIV PrEP efficacy trials with daily oral TDF–FTC[a] use

Study	Population	*n*	Modified intention to treat[b]			Self-report measures	Pill-count measures	TDF blood detection
iPrEx[5]	MSM	2499	44% (15%, 63%)			>50%[c] >90%	50% (18%,70%) 73% (41%, 88%)	92% (40%, 99%)
Partners PrEP[6]	Heterosexual HIV-discordant couples	4758 couples	All	Men	Women			
			75% (55%, 87%)	84% (54%, 95%)	66% (28%, 84%)	NR	100%[d] (87%, 100%)	90% (58%, 98%)
TDF2[7]	Heterosexual men and women	1200	All	Men	Women			
			62% (21%, 83%)	80% (25%, 97%)	49% (−21%, 81%)	NR	NR	NR
FEM-PrEP[8]	Heterosexual women	2056	NS			NR	NR	NR

Note: Values show percentage reduction in HIV incidence (95% CI).
[a]Restricted to trials of oral TDF–FTC only
[b]Modified intent-to-treat analysis excluding only those enrolled participants later found to be infected at randomization and those with no follow-up visit/HIV test
[c]A combined self-report and pill-count measure was used.
[d]In a substudy of participants who received supplementary adherence counseling if UPCs were <80%
FTC, emtricitabine; MSM, men who have sex with men; NR, not reported; NS, not significant; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate; UPC, pill counts at unannounced home visits

Bangkok Tenofovir Study. This study is evaluating the safety and efficacy of oral PrEP among injecting drug users in Thailand.[10] The trial is fully enrolled and results are expected to be released in late 2012.

Summary of Pre-Exposure Prophylaxis Clinical Trial Findings

The evidence for safety of daily oral TDF or TDF–FTC use among HIV-uninfected people is growing. The only consistent clinical adverse effects from PrEP have been minor gastrointestinal effects in a small proportion of users, particularly in the first month after starting PrEP. People were excluded from participating in clinical trials if they had certain pre-existing laboratory or clinical abnormalities that potentially could be worsened by exposure to PrEP medications. No major clinical toxicities in bone, renal, hepatic, or other systems have emerged, but longer-term follow-up has not been reported yet. More safety information is being collected in open-label studies and demonstration projects[12] that will increase understanding of who can safely take PrEP and how to optimally monitor the health of people on PrEP.

In each of the studies that showed efficacy,[5–7] the preventive effect was greater among participants with higher adherence to their drug regimen; in the FEM-PrEP trial, which found no efficacy, medication adherence was very low (Table 2). The success of PrEP in some trials and its failure in others to date is believed to most likely be due to low adherence, and suggests an urgent need to learn the reasons for participant failure to adhere and the best means to keep adherence high. This information will be critical to its implementation in HIV prevention programs.

Infection with HIV resistant to TDF and/or FTC was seen only among a few enrollees whose HIV infection was not detected at enrollment (i.e., those with negative HIV antibody tests at enrollment who were later determined to have been HIV infected by further testing of their stored, enrollment blood specimens). Viral resistance among those who become infected while taking PrEP medication must continue to be studied as PrEP is implemented. These initial PrEP trials excluded participation by pregnant women, breastfeeding women, and adolescents. Therefore, PrEP safety and efficacy for these populations is currently unknown.

Knowledge, Attitudes, and Use of PrEP for HIV Prevention

Several U.S.-based studies have assessed knowledge, attitudes, and potential use of PrEP for HIV prevention among at-risk populations and healthcare providers. Findings from these studies increase understanding of PrEP knowledge, use, and anticipated changes in sexual risk behaviors prior to broader implementation.

Searches of two online databases (PubMed, ISI Web of Science) and the CDC's HIV/AIDS Prevention Research Synthesis (PRS) database of the HIV behavioral prevention research literature[13] identified published studies on PrEP knowledge, attitudes, intentions, and use. Fourteen studies[14–28] reported PrEP knowledge and use among mostly MSM populations; two studies[29,30] reported PrEP attitudes and interest among heterosexual sexually transmitted disease (STD) clinic populations; and three studies[31–33] reported healthcare providers' knowledge and willingness to implement PrEP. No studies targeted injection drug users.

Nearly one quarter (23.1%) of all respondents surveyed in 14 studies conducted from 2004 to 2011 had some knowl-

edge and awareness of PrEP (Table 3). A study of gay bathhouse patrons in New York City reported that more than one third (36.3%) of respondents had knowledge of both PrEP and non-occupational post-exposure prophylaxis (nPEP).[21] Few respondents (range 0% to 7.0%) in these studies reported actual PrEP use. This is not unexpected given that the majority of studies occurred prior to the publication of the iPrEx trial results in November 2010.[5]

A study of MSM recruited from an Internet social-networking site and conducted 2 months before and 1 month after release of the iPrEx trial results (September 2010 to January 2011) reported a slight increase in PrEP awareness/interest before and after release of the iPrEx findings (12.5% vs 19%), but actual PrEP use remained very low (0.7% vs 0.9%).[26] Additional studies are needed to assess PrEP awareness and use among representative samples of MSM and at-risk heterosexual populations now that the PrEP trial results are known. Once the trial results for injection drug users are released in late 2012,[10] it will be important for future studies to assess PrEP knowledge, attitudes, and potential use in this population.

Several studies listed in Table 3 reported associations between sexual risk behaviors and knowledge of PrEP. In a study of MSM attending minority gay pride events in seven U.S. cities, those who had ever tested for HIV and those with ten or more male anal sex partners reported greater knowledge of PrEP and PEP.[24] In a cross-sectional survey of MSM in California, men who reported unprotected anal sex or engaged in sex while on drugs were more likely to be aware of PrEP than men not engaging in these behaviors.[19] Krakower et al.[26] reported that MSM Internet users' interest in PrEP was associated with older age, unprotected anal sex with one or more male partners during the past 3 months, and perception of oneself as being at increased risk for HIV acquisition.

Studies also examined demographic and behavioral factors associated with self-reported PrEP use. Among attendees at minority gay pride events, predictors of PrEP use included being African-American; having an HIV test during the past year; not meeting sex partners at bars, clubs, or through websites; and distrust of HIV prevention information from healthcare providers.[27] Golub et al.[17] reported that MSM in New York City were more likely to use PrEP if they engaged in recent high-risk sex acts, had greater belief that substance use enhances sex, and reported arousal barriers when using condoms.

In a study of MSM enrolled in an intervention efficacy trial in four U.S. cities, HIV-negative men who reported believing that the availability of HIV treatment lessened their concern about HIV were nearly six times as likely to use PrEP than their counterparts not reporting this belief.[20] In a large national sample of Internet users, PrEP users were at greater odds of having sex with both men and women (versus men only), having unprotected anal sex with at least one male partner in the past 3 months (versus no unprotected anal sex), being aware of PEP, and prior use of PEP.[26]

Concern has been expressed in the literature that PrEP use could increase the acquisition of HIV because of decreases in traditional HIV prevention strategies.[34] Several studies investigated the possibility of sexual risk compensation (i.e., increased number of sex partners and reduced consistent condom use) associated with hypothetic PrEP use. In a study of high-risk HIV-negative MSM in New York City, more than 35% of those willing to take PrEP reported they would decrease their use of condoms.[17] Qualitative interviews with 25 serodiscordant couples revealed a belief that adoption of PrEP provides an opportunity for engaging in unprotected sex.[15]

In contrast, an HIV behavioral surveillance survey of 425 HIV-negative MSM conducted in Denver indicated that only 7% of respondents were willing to decrease their condom use while taking PrEP.[25] Results of focus groups with African-American young adults in Atlanta revealed a willingness to consider PrEP as a method of prevention and belief that PrEP would not affect their use of condoms. However, MSM respondents expressed fears of behavioral risk compensation.[35]

Three studies[31–33] surveyed physicians and other healthcare providers on their knowledge and willingness to use antiretrovirals for PrEP. Although most providers were aware of PrEP, few had prescribed PrEP because of low demand from their patients. In all three studies, providers were concerned about PrEP safety, efficacy, adherence, and cost[31–33]; impact on other effective forms of HIV prevention (e.g., condoms)[32]; increased risk of HIV transmission if not completely effective[32]; and provision in primary care settings where providers can discuss sexual behaviors with patients in a nonstigmatizing manner.[31] According to providers working in STD and family planning clinics, PrEP could be an effective tool to empower at-risk women who are unable to negotiate consistent condom use with their male sex partners.[32] Providers recommended that PrEP implementation should be accompanied by practice guidelines on screening for risk among various populations, provision of training programs for providers to alleviate concerns about safety and efficacy, and community education campaigns for at-risk populations to reduce stigma associated with accessing HIV-related prevention services.[31,32]

Summary of Pre-Exposure Prophylaxis Knowledge and Use Studies in the U.S.

Studies of PrEP knowledge and use suggest that some members of at-risk populations, particularly MSM, have been aware of PrEP (and nPEP) for some time, but very few people reported actually using PrEP. A pattern emerged across studies that at-risk MSM with knowledge and prior

Table 3. Studies investigating knowledge and use of HIV pre-exposure prophylaxis in the U.S., 2004–2011

Study	HIV risk group	Location	*n*	PrEP knowledge (%)	PrEP use (%)
Kellerman (2004)[27]	80% gay/bisexual	Baltimore MD	104	20	6.8
	18% heterosexual	Detroit MI	170	19	2.0
		Oakland CA	139	18	1.6
		San Francisco CA	628	29	7.0
		Overall	1041	25	5.0
Voetsch (2005–2006)[24]	MSM	Charlotte NC	63	25.4	NR
		Chicago IL	82	14.6	NR
		Detroit MI	49	12.2	NR
		Jackson MS	32	9.4	NR
		San Francisco CA	35	22.8	NR
		St. Louis MO	34	23.5	NR
		Washington DC	102	21.6	NR
		Overall	397	18.9[a]	<1.0[a]
Koblin (2004–2005)[18]	MSM	New York City NY	503	NR	2.0[a]
Nodin (2006)[23]	MSM	New York City NY	72	0.3	NR
Liu (2006)[19]	MSM	San Francisco CA	403	20.0	NR
		San Diego CA	363	16.0	NR
		Overall	766	18.0	1.7
Mansergh (2006–2008)[20]	MSM	Chicago IL	NR	NR	NR
		New York City NY	NR	NR	NR
		San Francisco CA	NR	NR	NR
		Overall	454[b]	NR	2.0
Mehta (2006–2007)[21]	MSM	New York City NY	554	36.3[a]	0
Mimiaga (2007)[22]	MSM	Boston, MA	227	18.9	<1.0
Golub (2007–2009)[17]	MSM	New York City NY	180	23.2	1.7
Al-Tayyib (2008)[25]	MSM	Denver CO	425	21.4	NR
Barash (2009)[14]	MSM	Seattle WA	215	22.3	2.0
Whiteside (2009–2010)[29]	90% heterosexual (56% male) 8% gay/bisexual	Columbia SC	27[c]	22.2	NR
Brooks (2009)[15,16]	MSM	Los Angeles CA	50	0.0	0.0
Bautista (2011)[28]	MSM	Atlanta GA	418	30.0	2.0
Krakower (2010–2011)[26]	MSM	U.S. sample[d]			
		Pre-iPrEx results	289	12.5	0.7
		Post-iPrEx results	3387	19.0	0.9
		Overall	3676	18.5	0.9

[a]Measured PrEP or PEP knowledge/use among HIV-negative or unknown-status MSM; percentage could be elevated because of PEP knowledge/use
[b]HIV-negative subsample (454 of 1011 MSM)
[c]MSM subsample (27 of 358)
[d]Members of a large social-networking Internet site for MSM stratified by pre- and post-iPrEx results
MSM, men who have sex with men; NR, not reported; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis

use of PrEP were more likely to perceive themselves to be at risk for HIV and engage in risky sex behaviors. Among selected groups of physicians and other healthcare providers, most were knowledgeable about PrEP and many had concerns regarding safety, efficacy, cost, and risk compensation. Cross-sectional and longitudinal studies are needed to monitor, and assess interest in, actual use of PrEP and resulting changes in sexual behaviors as it is implemented with high-risk populations, including MSM, HIV-discordant couples, and injection drug users.

Cost Effectiveness of Pre-Exposure Prophylaxis

Implementation concerns have been raised about the high cost of PrEP with TDF–FTC.[36] A recent estimate[37] placed the monthly cost of TDF–FTC in the U.S. at $607. The published cost-effectiveness studies regarding PrEP made many assumptions regarding the long-term adherence to PrEP, development of resistant mutations, and risk compensation while taking PrEP, factors that can substantially influence cost-effectiveness estimates.

Desai et al.[38] used a mathematical model to evaluate the effect of a PrEP intervention targeting high-risk MSM in New York City. Their model predicted that when PrEP was used by 25% of high-risk MSM, it reduced the number of new infections from 19,510 to 17,800 (8.7% reduction) with a cost-effectiveness ratio of $31,972/quality-adjusted life-years (QALYs) saved. Paltiel and colleagues[39] estimated PrEP's impact on a high-incidence population (1.6% incidence per year) assuming 50% efficacy of PrEP. They reported a cost-effectiveness ratio of $298,000/QALY.[39]

Koppenhaver et al.,[40] using both a low-risk and high-risk population of MSM in New York City, reported a 61% decrease in new infections over 20 years with cost-effectiveness ratios of $570,273/QALY saved and $870,590/infection averted. Performing sensitivity analysis using the case in which patients are highly adherent (resulting in 73% efficacy) to PrEP, they reported an 86% decrease in new infections and cost-effectiveness ratios of $353,739/QALY saved and $631,791/infection averted.[40] More recently, Juusola et al. explored the impact of PrEP interventions targeted at the general MSM population, as well as a high-risk subpopulation.[41] They reported a cost-effectiveness ratio of $216,480/QALY when targeting only the high-risk subpopulation.[41]

The results of PrEP modeling studies were highly dependent on their assumptions and inputs. Initial prevalence, drug costs, efficacy, coverage, testing rates, and targeting all had significant impacts on incidence and cost effectiveness. In particular, interventions that targeted high-risk patients reported better cost-effectiveness ratios. Targeted PrEP interventions have the potential to greatly improve the cost effectiveness of PrEP programs in terms of both cost per QALY saved and cost per infection averted. Until further studies are conducted, informed by data from studies of actual PrEP use, it is not possible to know the true cost effectiveness of PrEP.

Conclusion

Daily oral PrEP with TDF–FTC can safely and effectively reduce the risk of HIV infection among uninfected MSM and among heterosexual women and men, particularly those in sexual partnerships with people known to have HIV infection. Models suggest that PrEP may be cost effective when targeted to the people at highest risk in these populations. However, studies of safety and efficacy of daily PrEP have been conducted mostly outside the U.S., and evidence of efficacy among heterosexual women beyond those in HIV-discordant couples is mixed. Ongoing and planned trials[12] will provide greater understanding about the safety and efficacy of daily oral TDF–FTC as PrEP in injection drug users, use of different drugs, delivery methods, and dosing schedules.

General awareness and use of PrEP was low in the U.S. prior to 2012, but interest in using it has been reported by people at substantial risk of HIV acquisition. Open-label studies and demonstration projects that evaluate how PrEP is implemented and used in U.S. community settings can inform clinical providers and public health officials on how best to deliver PrEP as a safe, targeted, and effective prevention intervention to reduce HIV infection.[42,43]

Publication of this article was supported by the CDC through the Association for Prevention Teaching and Research (CDCAPTR) Cooperative Agreement number 11-NCHHSTP-01.

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The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the CDC.

No financial disclosures were reported by the authors of this paper.

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