Pre-exposure Prophylaxis for the Prevention of HIV Transmission to Women in the United States

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The FDA recently approved a new pre-exposure prophylaxis (PrEP) indication for emtricitabine/tenofovir for men *and women,* allowing a new effective HIV prevention intervention. Recent clinical trials have demonstrated the efficacy of PrEP in reducing the risk of HIV acquisition among women. Its efficacy depends largely on adherence. Perception of HIV risk appears to drive adherence to PrEP. What motivates PrEP use is specific to the population and its unique vulnerabilities. Future interventions exploring the efficacy of PrEP must include a behavioral arm that is specific to the unique vulnerabilities of the population being studied.

There are an estimated 140,000 heterosexual serodiscordant couples in the US; approximately half of these couples desire conception. HIV-uninfected women in serodiscordant couples seeking conception may prove to be an ideal population for PrEP. Periconceptional PrEP in highly motivated couples could be not only effective but also affordable and feasible.

In order to make PrEP accessible to those populations most vulnerable to HIV infection the following steps need to occur: PrEP needs to be affordable particularly for those uninsured; HIV providers, primary care practitioners and reproductive healthcare providers need to welcome PrEP as a component of their scope of practice; clinicians need to take adequate sexual histories of all their patients in order to identify those at risk and best candidates for PrEP; identifying ways to promote adherence must include population specific PrEP adherence interventions.

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On July 16, 2012 the FDA approved emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) as pre-exposure prophylaxis (PrEP) to prevent HIV acquisition in adult men and women. While no single tool will be enough to stop the spread of HIV, PrEP should now become a vital part of a comprehensive, global strategy to end the epidemic. PrEP will help address important gaps in the current prevention toolkit, including the need for female-controlled biomedical interventions that can be used without partner involvement. The implementation of PrEP as a public health measure will require clinical monitoring, evaluation of successful adherence interven-

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Table 1. Impact of Drug Exposure on efficacy of PrEP.

Study	Population	N	Reduction in HIV Acquisition	Impact of Drug Exposure/Adherence
Partners PrEP (FTC/TDF)	Heterosexual discordant couples	4758 couples	75%	90% in subjects with detectable drug levels (random subgroup of 198 participants) (6)
CDC TDF2 (FTC/TDF)	Heterosexual Men & Women	1219	62.2%	50% of those who seroconverted had detectable plasma drug level. Of 69 matched samples who remained uninfected, 80% had detectable levels of TDF
Fem-PrEP (FTC/TDF)	Heterosexual	2120	Study stopped early for futility	Of those who seroconverted, 15%–26% on FTC/TDF had detectable drug levels; of those who remained HIV negative, 24%–35% had detectable drug levels; adherence was too low to assess efficacy

tions aimed at specific populations, and broadening access to care for HIV-exposed adults, establishing the cost per infection averted, and determining the feasibility of full-scale implementation in target populations,

There is now an array of interventions to choose from to prevent HIV transmission and acquisition. The CDC's strategy of "High Impact Prevention" involves a combination of HIV prevention interventions including antiretroviral therapy (ART) for all HIV-infected adults, antiretroviral prophylaxis in the form of PrEP and/or post-exposure prophylaxis (PEP) for HIV-exposed persons, treatment of sexually transmitted infections (STIs), circumcision, wide scale condom distribution, adherence counseling, behavioral change interventions, wide scale HIV testing programs, and linkage and retention to care.

(Table 1)

The HPTN 052 trial demonstrated ART to be a powerful tool for both HIV treatment and prevention, reducing the likelihood of HIV transmission by 96% [1]. However, intermittent HIV viremia not detected by episodic plasma viral load monitoring as well as suboptimal ART adherence by the HIV-infected partner may justify the concurrent use of PrEP for the at-risk HIV-uninfected partner.

Numerous studies have now demonstrated that PrEP also dramatically reduces the risk of HIV acquisition, including among women, with minimal risk of incident ART resistance. The Partners PrEP trial, conducted among 4758 HIV- serodiscordant heterosexual couples in Kenya and Uganda, demonstrated that daily TDF and daily TDF/FTC reduced the overall risk of HIV acquisition by 67% and 75%, respectively [2]. Among women the efficacy of TDF and TDF/FTC was 71% and 66%. Of the 96 persons who seroconverted, 8 were found to have been infected at randomization. No participants who acquired HIV after randomization had ART resistance. Efficacy seemed largely driven by adherence to PrEP. Among the 29 subjects with incident HIV who underwent drug level testing, only 31% had detectable TDF level in a plasma sample obtained at the seroconversion visit compared to 82% of a random subgroup of 198 participants who remained HIV-uninfected [2]. The CDC TDF2 trial compared TDF/FTC to placebo among 1219 heterosexual individuals in known serodiscordant relationships in Botswana. The overall protective efficacy was 62% and prevented HIV in both men and women. One participant had unrecognized acute HIV infection at the time of enrollment and developed resistance to the study medications. As with Partners PrEP, drug level measurements demonstrated that adherence to the regimen was associated with greater efficacy. Moreover, PrEP was found to be safe and well-tolerated by participants in these trials [3]. There was no evidence of a difference in efficacy by sex or power to detect sex difference found in the both the above studies Table 2.

Not all PrEP trials involving women have demonstrated efficacy however, and the conflicting results are critical to understand. The multicenter FEM-PrEP trial found that TDF/FTC did not effectively reduce the risk of HIV

Table 2. Efficacy by Gender.

TDF2 Efficacy- HIV Infection by Gender Using 33 Seroconverters	Efficacy	95% CI	P-Value	Interaction P-value
Female	49.4%	−21.7, 80.8	0.107	
Male	80.1%	24.6, 96.9	0.026	
Using 23 Seroconverters	Efficacy	95% CI	P-Value	Interaction P-value
Female	75.5	23.8, 94.4	0.021	
Male	82.4	−2.8, 99.1	0.065	
Partners PrEP Sub-Analysis by Gender				
TDF				
Women	68%	29%–85%	0.01	0.54
Men	55%	4%–79%	0.04	0.54
FTC/TDF				
Women	62%	19%–82%	0.01	0.24
Men	83%	49%–94%	0.001	0.24

Baeten J et al. 2011 IAS Rome, Italy Abs. Thigpen M et al. 2011 IAS Rome, Italy WeLBC01

Table 3. Effective Prevention Options.

Prevention Method	Strengths	Limitations
Condoms	Failure rate with perfect use: 2% male/5% female; Typical use failure: 15% male/21% female	Unreliable usage; Male controlled
PrEP for HIV uninfected partner	Up to 75% reduction in HIV acquisition	Effectiveness dependent on adherence; Resistant virus if seroconversion
ART for HIV infected partner	96% reduction in HIV transmission	Discordance in plasma and seminal fluid VL; Suboptimal adherence; Intermittent viremia
nPEP		
Circumcision	50–60% reduction in HIV acquisition	Not studied in US
Treatment of STIs		
Behavioral Interventions	>70 randomized studies showed behavioral interventions reduce risk behavior or STI acquisition	
Periconception Prevention	Sperm Washing and IUI – highly effective in prevention of HIV transmission	Not covered by most insurances; Highly expensive; Difficulty accessing services in the US
Opt-out HIV testing	Decrease in risk behavior once HIV status is known	Linkage to care and retention are not optimized
ART for perinatal transmission prevention	<1% transmission rate with ART and undetectable VL	Patient must access prenatal care
Sperm washing and artificial insemination	Highly effective in preventing HIV transmission	Financial barriers; Not widely available in the US

acquisition compared to placebo among 2056 high-risk women [4]. The estimated cumulative probability of infection at 12 months was 0.049 in the TDF-FTC group and 0.046 in the placebo group, This acquisition was likely due to suboptimal adherence to PrEP given that only 15 - 26% of women with incident HIV infection had drug levels suggestive of consistent TDF use [4]. Suboptimal adherence was likely driven in part by perceived low risk of HIV acquisition; 75% of the FEM-PrEP study participants reported not considering themselves at risk for HIV. While the FEM-PrEP results were disappointing, these data are immensely illuminating and highlight the importance of identifying appropriate candidates for PrEP and the need to further evaluate effective counseling and adherence interventions. It is clear that efficacy of PrEP depends on adherence to the medication. Motivation to take a daily medication is likely tightly interwoven with risk perception. Future studies evaluating the efficacy of PrEP should include an assessment of motivation and vulnerabilities to adherence to PrEP for at-risk populations.

(Table 3)

While PrEP efficacy trials involving women have been conducted in high HIV prevalence settings in sub-Saharan Africa, it is important to understand the relevance of these data to specific populations of women at risk of HIV acquisition in the US. Heterosexual sex is the primary mode of HIV transmission among women, particularly women of color, in the US with approximately 90% having acquired HIV through heterosexual contact [5]. One population that could particularly benefit from PrEP is HIV-infected male/HIV-uninfected female couples seeking conception. There are an estimated 140,000 heterosexual serodiscordant couples in the US and approximately half of these couples desire conception [6,7]. While condoms are exceptionally effective at reducing the risk of sexual HIV transmission, they are counterproductive for couples who want to get pregnant. For most of these serodiscordant couples, logistical and financial barriers preclude the use of sperm washing with artificial insemination as a realistic safer conception option. Moreover, there are few fertility centers in the US willing to offer artificial insemination to serodiscordant couples in which the man is HIV-infected [8]. The use of periconceptional PrEP as an adjunct to suppressive ART for the HIV-infected male partner, may prove to be an ideal intervention for such couples unable to access or unwilling to undergo expensive, technology-intensive fertility services.

While data are limited, periconceptional PrEP appears feasible and acceptable. Vernazza and colleagues conducted an observational study in Switzerland among serodiscordant couples seeking conception where the male partner was HIV-infected with a suppressed viral load on ART and the female was HIV-uninfected. Of the 46 couples who chose periconceptional PrEP, 75% of couples successfully conceived by 12 months with no cases of incident HIV [9]. Additional studies are needed investigating use of PrEP outside of clinical trials in serodiscordant couples to access attitudes towards the use of PrEP among clinicians and patients and adherence in order to allow a proper understanding of the potential efficacy of and adverse events associated with PrEP and to identify other factors that might influence efficacy.

Overall, safety data on the use of TDF/FTC during pregnancy are reassuring. Extrapolating from data among HIV-infected women, first trimester TDF/FTC exposure appears safe [10]. The International Antiretroviral Pregnancy Registry has found no association between the use of first-trimester TDF/FTC and congenital anomalies. For both drugs the registry has collected sufficient first trimester exposure data to rule out at least a two-fold increased risk of overall birth defects.

Now that the FDA has done their part in expanding HIV prevention interventions available to men and women in the United States, it is up to clinicians, policy makers, government agencies, Gilead Sciences, insurance com-

panies and consumers to roll out this new prevention tool. In order to allow PrEP to be accessible to and effective among those populations most vulnerable to HIV infection the following needs to occur:

(1) *Financial Coverage of PrEP*: The cost of TDF/FTC must be affordable for insurance companies, government benefit programs and paying consumers. Health insurances should cover PrEP without imposed time-constraining barriers such as prior authorization requirements. Drug assistance programs must be assured for uninsured persons, many of whom are the most vulnerable to HIV acquisition. Coverage needs to be ensured as part of a prevention package through the Affordable Care Act.
(2) *Clinicians should prescribe PrEP to appropriate candidates*: The inclusion of PrEP needs to be part of an array of HIV prevention services that are available at HIV, primary care, gynecology and family planning clinics. At-risk HIV-uninfected patients and sexual partners of known HIV-infected patients should be welcomed into clinical practices. HIV providers, primary care practitioners and reproductive healthcare providers who encounter patients at risk of HIV acquisition need to have PrEP as a component of their scope of practice.
(3) *Identification of those most at risk of HIV acquisition*: Key to its success is the identification of appropriate candidates for PrEP. While some resourceful HIV-uninfected patients who could benefit from PrEP will seek out this intervention, providers cannot rely on passive recruitment. In order to identify those who could benefit most from PrEP, clinicians need to take adequate sexual histories of all HIV-infected patients including asking about HIV status of sexual partners, disclosure of HIV status to sexual partners, and reproductive desires.
(4) *Identifying ways to promote adherence*: Perception of risk appears to be a key predictor of adherence. Specific PrEP adherence interventions have not yet been fully studied. Other interventions shown to enhance ART adherence include couples counseling [11], text-message reminders, motivational interviewing [12], ART adherence counseling, risk reduction interventions [13], home based nursing visits, substance abuse therapy and strengthening social support. It is possible that the lessons we have learned from the contraception literature will be helpful. We have been successful in helping healthy individuals take a daily pill to prevent pregnancy. We know that long-acting methods are more effective and associated with improved adherence. It is welcomed news that new PrEP formulations, including injectables and vaginal rings, are being actively studied.

In over 30 years of battling this epidemic, we have learned that a combination of proven preventive approaches targeted at specific populations, including evidence based biomedical and behavioral strategies, is the most effective way to decrease incident HIV infections. Interventions need to be prioritized and tailored to the specific circumstances of individual patients. Female controlled interventions give women choices and are a critical component of HIV prevention efforts. In order to reach the goal of the National HIV/AIDS Strategy of reducing the current annual HIV incident of 50,000 infections by 25% in 5 years, we must embrace all effective prevention tools towards the goal of eliminating sexual HIV transmission. PrEP is now a vital part of a global strategy to end the epidemic.

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Conflicts of interest

The author(s) report(s) no real or perceived vested interests that relate to this article (including relationships with pharmaceutical companies, biomedical device manufacturers, grantors, or other entities whose products or services are related to topics covered in this manuscript) that could be construed as a conflict of interest.

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