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Review of real-world implementation data on emtricitabine-tenofovir disoproxil fumarate as HIV pre-exposure prophylaxis in the United States

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Abstract

The antiretroviral combination of emtricitabine-tenofovir disoproxil fumarate (FTC/TDF) was approved by the United States Food and Drug Administration (FDA) for use as Pre-Exposure Prophylaxis (PrEP) in individuals at high risk for acquiring human immunodeficiency virus (HIV) in July 2012. Since then, Centers for Disease Control and Prevention (CDC) guidelines for the use of PrEP have been published and implemented into clinical practice throughout the United States. A number of published open-label and PrEP demonstration projects have evaluated the real-world use of PrEP including analysis of the barriers to its use and addressing major concerns. Despite the approval of FTC/TDF for PrEP, its use for this indication is reliant on patient and provider acceptance, and its effectiveness requires patient adherence and retention in care during periods of high-risk behaviors. Concerns regarding the use of PrEP in healthy individuals persist and include medication adverse effects, including renal dysfunction and bone mineral density loss; risk compensation leading to HIV infections, sexually transmitted infections, and unintended pregnancies and the development of drug resistance in the event of seroconversion. The cost effectiveness of PrEP continues to be assessed with the greatest cost effectiveness remaining in those at highest risk of acquiring HIV. Additionally, cases of HIV acquisition in individuals who are adherent to PrEP highlight scenarios in which PrEP is not 100% effective, including against the transmission of drug-resistant HIV strains. This review examines data on the implementation of PrEP outside the setting of clinical trials with the aim of providing clinicians with a summary of the current barriers and opportunities for PrEP use with a specific focus on the role of pharmacists in optimization of PrEP implementation.

Keywords

HIV; pre-exposure prophylaxis; emtricitabine; tenofovir disoproxil fumarate

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Conflict of Interest

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Introduction

According to the Centers for Disease Control and Prevention (CDC), the number of new human immunodeficiency virus (HIV) infections in the United States fell 18% between 2008 and 2014 from approximately 45,700 to 37,600.¹ Although efforts were made during this time period to increase testing, initiate antiretroviral therapy (ART) in all those infected, and encourage viral load suppression, pre-exposure prophylaxis (PrEP) also became available as a way for at-risk individuals to protect themselves from contracting HIV. In 2012, the US Food and Drug Administration (FDA) approved Truvada[®] (emtricitabine-tenofovir disoproxil fumarate 200 mg/300 mg or FTC/TDF) taken orally once daily for PrEP in high-risk HIV-negative individuals in combination with safer sex practices. The FDA based approval on three large randomized, double-blind, globally conducted, placebo-controlled, clinical trials that demonstrated efficacy in preventing HIV infection in HIV-negative individuals.^{2–4} The CDC guidelines for the use of PrEP for the prevention of HIV thoroughly summarizes these trials, demonstrating high rates of efficacy in adherent patients.⁵ As of the beginning of 2017, an estimated 120,000 individuals initiated PrEP. However, the CDC estimates more than 1.2 million people living in the United States have an indication for PrEP.⁶ Data from 2012 to 2016 suggest that an increasing number of PrEP prescriptions during this time frame led to a decrease in HIV diagnoses; however, patient and provider acceptance, adherence and retention, adverse effects (AEs), concerns for behavioral risk compensation, resistance development with HIV acquisition, and cost effectiveness remain as potential barriers to the successful implementation of FTC/TDF for PrEP in real-world settings.^{6,7} The purpose of this review is to describe the implementation of FTC/TDF as PrEP in the United States since FDA approval for this indication in 2012. This review explores the barriers and successes to PrEP use in the real world and makes recommendations for the pharmacist's role in providing PrEP care.

Methods

In order to review the literature surrounding the implementation of FTC/TDF for PrEP in real-world settings, a PubMed search was conducted using combinations of search terms that included HIV, pre-exposure prophylaxis, and emtricitabine and tenofovir. These terms were then combined with each of the subheadings below (i.e., adherence, resistance, acceptance, seroconversion, cost-effectiveness). Additionally, abstracts were reviewed from relevant conferences including The Conference on Retroviruses and Opportunistic Infections (CROI), The International AIDS Conference (AIDS), The International AIDS Society (IAS) Conference on HIV Science, IDWeek, and HIV Research for Prevention (HIVR4P). Recent abstract or conference presentations were only included if judged to be of novel or significant impact. Data included was limited to the real-world implementation of FTC/TDF for PrEP in the United States, and therefore modeling studies were excluded, with the exception of modeling of cost-effectiveness scenarios. All studies found since the FDA approval of FTC/TDF for PrEP in July 2012 were considered through July 2018. All large scale demonstration projects and open-label extensions were included to evaluate the data surrounding the challenges to PrEP implementation including potential AEs, adherence and retention, risk compensation, and resistance. Table 1 summarizes the large demonstration projects discussed throughout.^{8–10} Additional smaller scale surveys, descriptive reports, and

case studies were included to evaluate patient and provider acceptance of PrEP, the development of HIV infection in patients on PrEP, and current pharmacy practice as it relates to PrEP.

Discussion

Patient Acceptance

A key criterion for the implementation of PrEP in the real world is the willingness of healthy individuals to take daily FTC/TDF for PrEP. The majority of data on the acceptance of PrEP is from survey studies of men who have sex with men (MSM) (See Table 2).^{8,11–13} Uptake of Pre exposure Prophylaxis, Sexual Practices, and HIV Incidence in Men and Transgender Women Who Have Sex with Men: A Cohort Study (iPrEX OLE) was a 72-week open-label extension study of The Pre exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men (iPrEX) study and two other PrEP studies that took place in the United States, Brazil, Peru, Ecuador, South Africa, and Thailand (Table 1).⁸ Prior to FTC/TDF initiation within the iPrEX OLE study, MSM and transgender women were given a questionnaire to gauge desire to use PrEP.⁸ The questionnaire was provided to 1603 participants eligible for PrEP, of which, 1230 (77%) wanted FTC/TDF as PrEP. Reasons patients declined PrEP were concerns regarding side effects (50%), daily pill burden (16%), not wanting to take pills (13%), inclination to alternative prevention methods (14%), and fear others would think they had HIV (10%). Participants who communicated a lack of condom use at the time of anal intercourse were more willing to use PrEP (416/519 81%; $p = 0.003$). Other surveys of MSM have found that men were more likely to think PrEP was a good prevention strategy for themselves if they were in serodiscordant relationships with a known partner living with HIV and although large percentages of MSM expressed interest in PrEP, lower percentages actually initiated PrEP when offered.^{11,12} The most common reason for disinterest was that the participants were already consistently using condoms and those who did not initiate PrEP were more likely to affirm, “I would be unhappy about taking a pill every day” compared to those who did initiate PrEP ($p=0.002$).¹² In a large national online survey of 4698 MSM, 85% had never used PrEP although only 22% were unaware of PrEP.¹³ Of 2926 non-users who demonstrated a high knowledge of PrEP, reasons for non-use were concerns about cost (40%), side effects (31%), effects on insurance (20%), and/or not feeling at risk (19%). Although transgender women are often included with MSM in PrEP studies, their awareness of PrEP may be lower and interest in PrEP complicated by distrust of medical professionals.¹⁴

Less information exists about the PrEP acceptance among at-risk women compared to MSM and only about 10% of PrEP prescriptions in 2016 were for women.⁶ However, out of 2590 adolescents aged 12 to 17 years who initiated PrEP from 2012 to 2017, 84% were girls.²⁹ Focus groups of women taking PrEP indicated that PrEP allowed them to remain healthy, improved intimacy with their partners, and reduced their anxiety of becoming HIV infected. However, they did report feeling there was stigma surrounding their PrEP use.¹⁵ Women not yet on PrEP, expressed limited knowledge about PrEP and concerns about side effects, cost, the possibility for resistance, misuse, effect on pregnancy, stigma, and long-term effects of

PrEP use.^{16,17} They identified barriers to use including competing priorities, lack of partner support, and judgement from providers.

There is also limited data on patient acceptance of PrEP among intravenous drug users (IVDUs). A focus group with 20 IVDUs recruited from a methadone clinic found that the majority (95%) of participants had never heard of PrEP.¹⁸ These results were reinforced by a study of the National HIV Behavioral Surveillance System that found that only 9% of 188 IVDUs with an indication for PrEP in Washington, D.C. had ever heard of PrEP, and none had taken it.¹⁹ The concerns expressed by participants were that PrEP may encourage risky behavior, cost, side effects, drug interactions with methadone, the burden of a daily medication, and stigma. However, the majority of focus-group participants did say that they would be interested in trying PrEP.¹⁸

Acceptance and knowledge of PrEP is higher among MSM than any other risk group. It is becoming normalized as this population is increasingly targeted for marketing and prescribing. Women continue to voice concerns about stigma and fear of judgment that limit their desire for PrEP, although the rates of PrEP use in adolescent girls is outpacing that of adolescent boys. IVDUs lack awareness and knowledge of PrEP and have competing concerns regarding withdrawal and overdose, which may overshadow the concern for HIV acquisition. Targeted marketing and prescribing to women and IVDUs in the future could prevent additional HIV diagnoses in these populations. Health care providers, including pharmacists, should strive to increase awareness of PrEP in patients who may be at risk, ensuring eligible patients know they have varied options for HIV prevention, and counseling on the risks and benefits of PrEP compared to other prevention methods.

Provider Acceptance

Despite FDA approval of FTC/TDF for PrEP in 2012, prescriber acceptance also presents a barrier to use. A number of survey studies have been conducted assessing health care provider acceptance and concerns with PrEP (See Table 2).^{18,20–28} Most health care providers see PrEP as a viable prevention method, however few have actually prescribed PrEP (See Table 2 for specific prescribing rates).^{23–25,27,28} Concerns reported by providers include lack of efficacy, adherence, toxicities, increase in sexually transmitted infections (STIs), drug resistance, cost, insurance coverage, stigma, administrative logistics, and a lack of evidence in real-world settings. Knowledge about PrEP, lack of experience, and beliefs about who should be prescribing PrEP are also barriers to provider acceptance and prescribing of PrEP.^{18,20–28} HIV providers, infectious diseases specialists, non-HIV providers, public health departments, and STI clinics have all been suggested as potential prescribers of PrEP.^{24,25} Expanding PrEP prescribing beyond HIV and infectious diseases providers would increase access and availability to PrEP for at-risk individuals, however it is clear educational and awareness gaps exist.

Limited data is published about pharmacists' perception of their role in PrEP. Surveys conducted in Utah, Florida, and Minnesota have found that the majority of pharmacists are not familiar with the CDC guidelines for PrEP (Table 2).^{20–22} Most pharmacists did not feel comfortable counseling patients due to lack of knowledge about the medications used and indications for PrEP. Development of targeted continuing education opportunities, as well as

integration into pharmacy curriculum, is clearly needed to better equip the pharmacy workforce for PrEP.

At an organizational level, in a survey of 56 local health departments in North Carolina, only two (4%) had prescribed PrEP and seven (13%) had referred patients for PrEP services.²⁷ The majority of reasons cited by the health departments for not providing PrEP services were related to lack of resources and training. This indicates that enhanced training to rural and resource-limited settings that are heavily reliant on local health departments could have a significant impact on the HIV epidemic.

Health care professionals continue to debate who should be responsible for prescribing and following up with patients on PrEP according to the guideline recommendations. Although HIV providers are likely the most experienced with prescribing FTC/TDF, the patients who are eligible for PrEP do not have HIV and therefore may not find HIV providers accessible. Primary care providers (PCPs) may be more accessible but may also be less familiar with the use of the drugs themselves. One multicity survey found that only 17% of PCPs had ever prescribed PrEP compared to 64% of HIV providers.²⁸ Limited knowledge about PrEP and concerns about insurance coverage were the most common prescriber barriers mentioned. This may present a unique role for pharmacists who, under collaborative practice agreements, could provide both access and drug expertise. The most successful PrEP delivery system involves interprofessional engagement from prescribers, dispensers, and counselors between a variety of health care settings.

Adherence and Retention

The randomized clinical trials that provided evidence-based support for FTC/TDF in preventing HIV transmission showed a clear relationship between adherence and efficacy.²⁻⁴ Following the FDA approval of FTC/TDF for PrEP, adherence was evaluated in iPrEX OLE (Table 1).⁸ In 1225 participants who received PrEP, tenofovir diphosphate (TFV-DP) concentrations were measured via dried blood spots (DBS) at week 4, 8, or 12 and compared to HIV incidence rates. When no drug was detected (25% of visits tested), the HIV incidence rate was 4.7 infections per 100 person-years in contrast to 0.0 infections per 100 person-years when the estimated adherence rate was four or more doses per week (33% of visits tested) ($p < 0.0001$). Adherence was also assessed in the Adolescent Trials Network 110 Study (ATN 110) via TFV-DP and emtricitabine-triphosphate (FTC-TP) intracellular concentrations in DBS in 200 patients.⁹ In the first 12 weeks, 90% of participants had detectable TFV-DP in DBS, but concentrations decreased over the course of therapy. By week 48, 69% of participants had detectable concentrations present, but only 34% of participants had concentrations consistent with four or more doses per week. The most common reasons reported for missing medication doses were forgetfulness, being away from home, and being too busy. In the US PrEP Demonstration Project, adherence was measured at weeks 4, 12, 24, 36, and 48 by participant self-report, pill counts, and a calculated medication possession ratio (pills dispensed/days between visits) in 557 patients.¹⁰ Additionally, TFV-DP concentrations were measured with DBS at each follow-up visit for a subset of 294 patients. At 48 weeks, 78% of participants were retained in care. Adherence was very good or excellent by self-report at 87% of visits, 82% by pill counts, and 86%

according to the medication possession ratio. TFV-DP concentrations in DBS were adequate in 80% or more of samples at each measurement. Sixty-three percent of participants had TFV-DP DBS concentrations correlating to four or more doses per week at all visits and only 2.9% consistently had concentrations correlating to less than two doses per week. Other ongoing demonstration projects and refill data have identified predictors of adherence to PrEP to include age, race, sex, substance use, comorbidities, risk behavior, and partnership type.^{30,31} Overall, the adherence monitoring done in these studies indicate that adherence is better during times of higher perceived risk, although the large demonstration projects have found that on average adherence to PrEP wanes over time.

In the California Collaborative Treatment Group (CCTG) 595 Study, automated text messaging was explored as a strategy to address adherence to PrEP. Automated text messaging did not significantly increase the percentage of MSM with “adequate adherence” when measured by TFV-DP in DBS; however, after adjusting for age, there was a significant improvement in the percentage of MSM with “near perfect adherence”, suggesting text messaging is unlikely to provide significant benefit to those most at risk of nonadherence.³² Adherence counseling with a pharmacist has been shown to be highly effective in improving adherence and retention in the HIV treatment setting; applying these practices to HIV prevention may play a vital role in overcoming these barriers to adherence.³³

One strategy researchers have explored to address the concerns with adherence to daily dosing of PrEP has been the use of on-demand dosing around high-risk sexual activity. In the Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) study, 400 MSM were randomized to FTC/TDF or placebo taken before and after sex only.³⁴ Participants were instructed to take two tablets 2 to 24 hours before sex, one tablet 24 hours later, and then one tablet 48 hours later. A relative risk reduction of 86% (95% confidence interval [CI] 40–98; $p=0.002$) was reported for the FTC/TDF group with a median of 15 tablets taken per month. It is important to note that although this strategy was found to be effective in MSM, pharmacokinetic data and pharmacokinetic/pharmacodynamic modeling has raised concerns that drug concentrations in the female genital tract may not be adequate to allow for this dosing strategy to be effective in women.³⁵ In 2018, the IAS USA panel published updated HIV treatment and prevention guidelines that stated on-demand dosing was an alternative to daily PrEP for MSM with infrequent exposures.³⁶ For other risk groups, the recommended PrEP dosing strategy remains one tablet daily for FTC/TDF.

Alternative PrEP formulations are also being studied to minimize the effects of medication nonadherence on PrEP efficacy. A monthly vaginal ring containing the non-nucleoside reverse transcriptase inhibitor (NNRTI), dapivirine, was found to reduce the HIV incidence by as much as 56% in those 21 years of age and older when compared to placebo.³⁷ A long-acting injectable formulation of cabotegravir, an integrase inhibitor, dosed every 8 weeks is currently being compared to daily oral FTC/TDF for PrEP in clinical trials in both MSM and women (www.clinicaltrials.gov NCT02720094 and NCT03164564)^{38,39}. Additional longer-acting formulations of PrEP candidate agents are in earlier stages of development.⁴⁰ For patients who are unwilling or unable to adhere to a daily oral medication, these long-acting formulations may provide more appealing PrEP options.

Similar to adherence, retention in care is a factor requiring patient motivation that predicts PrEP success. One hundred seventy one HIV-negative participants from three established PrEP programs in Providence, RI, Jackson, MS, and St. Louis, MO were given PrEP for at least 6 months and followed every 3 months based on CDC guidelines.⁴¹ More patients were retained in care at 3 months (72%) than at 6 months (57%). Only one participant reported that discontinuation of PrEP was due to behavioral change at 3 months and three participants reported discontinuation for this reason at 6 months. At a county health department in Atlanta, only 39% of 201 patients remained in care 6 months after initiating PrEP.⁴² Similarly low rates of retention in care were found at a program in Los Angeles where 32% of the 1,764 individuals who initiated PrEP discontinued by 3 months and 45% discontinued by 6 months.⁴³ There were more HIV seroconversions in patients who discontinued PrEP compared to those who remained in care (6 patients vs 2 patients, respectively; $p=0.04$). Methods to keep at-risk individuals engaged in care should be part of any prevention service.

Adverse effects

When FTC/TDF is given as PrEP, there is a concern regarding AEs in otherwise healthy individuals.²³ Emtricitabine and TDF are commonly used as part of a three-drug regimen for the treatment of HIV and therefore the AEs and tolerability profile have previously been well described in the HIV-infected population. According to the prescribing information, general AEs associated with FTC/TDF include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, and rash (>10% occurrence); however, there is a risk for more serious AEs with the use of TDF including renal dysfunction and bone mineral density (BMD) loss.⁴⁴ Therefore, these AEs have been a focus of study with the use of FTC/TDF as PrEP.

The US PrEP Demonstration Project was an open-label study that enrolled 557 MSM and transgender women initiating FTC/TDF for PrEP in San Francisco, Miami, and Washington, D.C. (Table 1).¹⁰ By the first 12 weeks on FTC/TDF, serum creatinine (SCr) was found to have increased 0.03 mg/dl from baseline ($p<0.0001$), but remained stable thereafter up to 48 weeks.⁴⁵ This change correlated with a creatinine clearance (CrCl) decrease of 4.8 ml/min. Although statistically significant, this increase in SCr is unlikely to be of clinical significance. Proteinuria increased in 16% of participants from baseline in the first 12 weeks ($p<0.0001$), but remained stable through week 48. Greater adherence, as indicated by higher concentrations of TFV-DP in DBS, correlated with greater decreases in CrCl and was associated with a greater likelihood of worsening proteinuria. There was a significant difference in the mean CrCl change between those who had TFV-DP concentrations indicative of less than two doses per week compared to four to seven doses per week ($p=0.011$), suggesting that the TDF component of FTC/TDF was contributing to the CrCl decline in these participants.

Potential loss of BMD is also important, especially in otherwise young, healthy individuals. The ATN 110 study was an open-label demonstration project and phase II safety study that enrolled 200 MSM from 18 to 22 years of age from 12 urban US cities and gave them FTC/TDF once daily for PrEP (Table 1).⁹ Researchers examined BMD Z-scores in participants. Although these men had lower than expected mean BMD at baseline, a

statistically significant decrease in BMD was demonstrated by decreased Z-scores in the hip (-0.4% $p < 0.001$) and whole body (-0.6% $p < 0.001$), and modest, but not-statistically significant decreases in the spine (-0.2% $p = 0.11$) over 24 weeks. The participants did not experience any bone events.

Overall, AEs from FTC/TDF when taken for PrEP in HIV-negative populations appear to be similar to those seen in the HIV-infected population when taken for treatment. Because individuals initiating PrEP are often young and otherwise healthy, the risks associated with FTC/TDF should be weighed against its benefits for this indication. The potential for AEs should be considered and discussed with patients before initiating FTC/TDF for PrEP and laboratory markers for AEs should be followed closely while on PrEP.

Tenofovir alafenamide (TAF) is a new prodrug of tenofovir (TFV) approved for treatment of HIV infection in 2015 as it was shown to be noninferior to TDF-based regimens.⁴⁶ For HIV treatment, TAF appears to have a pharmacokinetic advantage over TDF; 25 mg per day of TAF achieves intracellular metabolite concentrations 7-fold higher than 300 mg per day of TDF, whereas plasma TFV concentrations are 86% lower.⁴⁷ In clinical trials and early use data, this reduced systemic exposure to TFV has led to a reduction in negative bone and kidney effects. This apparent safety advantage makes FTC/TAF an appealing alternative to FTC/TDF for use as PrEP; however, there is some concern regarding mucosal distribution of TAF. Following a single dose of oral TAF, intracellular TFV-DP concentrations in female genital and rectal tissues have been found to be 1.3- to 13-fold lower than those reported for TDF, with more unquantifiable concentrations in the TAF arm (35% more in female genital tract and 75% more in rectal tissue).⁴⁸ A randomized non-inferiority study between FTC/TAF and FTC/TDF for PrEP in MSM and transgender women is currently underway (www.clinicaltrials.gov NCT02842086) and will provide important insight into the use of TAF as a preventive agent.⁴⁹

Risk Compensation

With the increasing use of FTC/TDF for PrEP, there is a concern for a potential decrease in condom use, reduction in safe sex practices, and an increase in risky behaviors because of the perceived protective benefits. Risk compensation may increase the risk of HIV infection, other STIs, and unintended pregnancies. Risk compensation measures in the three large demonstration projects, iPrEX OLE, ATN 110, and The US PrEP Demonstration Project, are summarized in Table 1.⁸⁻¹⁰ Numbers of sexual partners and rates of condomless sex reported in these three studies did not increase on PrEP, and although overall STI rates were high, STIs did not necessarily increase with PrEP use. In iPrEX OLE and ATN 110, increased drug concentrations were correlated with reported high-risk sexual activity, indicating that the perceived risk of HIV acquisition may have been driving superior adherence in these participants.^{8,9}

Risk compensation while on PrEP likely did lead, however, to an increase in STI incidence in a study of 657 Kaiser Permanente members initiating FTC/TDF for PrEP.⁵⁰ Thirty percent of patients were diagnosed with a STI after 6 months on PrEP and 50% after 12 months, with a total of 344 diagnosed STIs during the study. Rectal STIs were diagnosed in 18% of patients at 6 months and 33% at 12 months. The most common STIs were chlamydia (6

months = 17%; 12 months = 33%) and gonorrhea (6 months = 15%; 12 months 28%). Despite the high STI rates, there were no incidences of HIV infection. A survey in a subset of 143 patients showed 41% reported a decrease in condom use whereas 56% reported no change in condom use from baseline. A smaller case-crossover study of 211 MSM using PrEP and living in Los Angeles compared STI rates before and after starting PrEP and found a statistically significant increase in the rates of syphilis and rectal chlamydia but no increases in rectal gonorrhea, pharyngeal gonorrhea, urethral gonorrhea, and/or urethral chlamydia after PrEP initiation.⁵¹

A study conducted by City University of New York researchers found an increase in reported condomless anal sex acts while on PrEP compared to before and after PrEP initiation in 313 MSM.⁵² There was an average of 2.8 condomless anal sex acts reported before PrEP use, 7.1 reported during PrEP use ($p<0.001$), and 2.1 reported after PrEP use ($p<0.001$). The authors concluded that these results indicate men in this study were using PrEP as it was intended (i.e., during periods of high-risk sexual activity). In contrast, a study of 953 young MSM in Chicago aged 16 to 20 years old (at time of enrollment) found an increase in number of total sex acts as well as number of condomless receptive anal sex acts when participants were on PrEP; this increase was consistent even among participants with inconsistent adherence.⁵³

Taken together, these results highlight the importance of (i) continued testing and monitoring for concurrent STIs while on PrEP and (ii) counseling patients to ensure they understand ongoing risks. PrEP is most effective when used as part of a comprehensive prevention package.

Resistance

Patients may seroconvert while on PrEP, and the resulting potential for resistance increases with increasing exposure to the suboptimal (for treatment) two-drug FTC/TDF combination. Once HIV infection is acquired, it is crucial that the patient be initiated on an optimal three-drug antiretroviral regimen to prevent drug resistance. However, data showing that the use of FTC/TDF for PrEP may lead to drug resistance is very limited.

In iPrEX OLE there were 28 HIV infections in those on PrEP.⁸ Of these, only one patient was found to have the M184V mutation, which confers resistance to FTC (and lamivudine). No infections occurred in those with DBS drug concentrations indicative of four to seven doses per week, and drug concentrations indicative of two to three doses per week were associated with a 90% risk reduction. It was evident that those who seroconverted had not been taking PrEP around the time of infection and therefore would have been unlikely to develop drug resistance. Among the 200 MSM between the ages of 18 to 22 years old who received FTC/TDF for PrEP in ATN 110, only four became infected with HIV (at weeks 4, 32, 40, and 48).⁹ None of the four individuals had detectable drug concentrations at the last measure prior to seroconversion and no drug resistance was identified. Two participants that seroconverted in the US PrEP Demonstration Project were further tested for resistance by genotyping and with minor variant assays.¹⁰ The first seroconversion was detected 19 weeks after PrEP initiation and the second was detected 4 weeks after the 48-week follow-up, when

FTC/TDF was no longer provided. Both patients had DBS TFV-DP concentrations indicating less than two doses per week and no resistance mutations were identified.

Development of resistance still poses as a possibility in patients taking FTC/TDF for PrEP who become infected with HIV, but there have been limited cases of this occurring, most likely because HIV seroconversion has most commonly been associated with non-adherence or transmission of multidrug-resistance strains (discussed further below).

Cases of HIV Acquisition on PrEP

It is important to highlight that FTC/TDF has never been found to be 100% effective at preventing HIV transmission in clinical trials or in studies of real-world use. There have been cases of HIV acquisition reported in patients who were likely adherent to FTC/TDF for PrEP.^{54–57} The first was a 43-year-old MSM who successfully took FTC/TDF for PrEP for 24 months prior to being infected with a multidrug-resistant HIV strain.⁵⁴ This patient was believed to have been adherent to PrEP at the time of HIV acquisition because he had consistent pharmacy dispensing records and adequate TFV-DP concentrations measured in DBS. A second case of HIV acquisition was in a male in his twenties with a known HIV-infected male partner suppressed on ART.⁵⁵ He tested positive for HIV 4 months into PrEP therapy despite claiming perfect adherence and having adequate TFV-DP concentrations in DBS and hair. His viral strain was not phylogenetically linked to his known virologically-suppressed partner, indicating he had been infected by someone else. Genotypic testing revealed resistance to FTC with the M184V mutation, TDF with the K65R mutation, and multiple NNRTI mutations. Each of these individuals likely acquired HIV strains that were resistant to FTC/TDF, rather than developing resistance by continuing to take PrEP after seroconversion.

A third case has been reported of a 34-year-old MSM who, when tested positive for HIV, was found to have resistance to FTC with the M184V mutation, resistance to TDF with the K65R mutation, as well as, NNRTI mutations.⁵⁶ This patient reported continual use of PrEP, but failed to follow-up for repeat HIV testing for more than a year so it is possible that he contracted a viral strain resistant to NNRTIs and then developed FTC and TDF resistance mutations with continued use of the two-drug ART regimen, rather than contracting a viral strain resistant to FTC, TDF, and NNRTIs. This patient had adequate FTC and TFV concentrations in plasma, and segmented hair concentrations were consistent with daily dosing during the 3 months prior to HIV diagnosis.

A fourth case of a 50-year-old MSM who tested positive for HIV 8 months after initiating FTC/TDF for PrEP, was the first transmission reported of a wild-type strain of HIV, without the presence of resistance mutations.⁵⁷ This patient had high TFV-DP concentrations in DBS at both 6 and 8 months, indicating adequate adherence. These cases demonstrate the importance of the CDC recommendation to provide PrEP as part of a comprehensive prevention package.⁵ Patients should be made aware that PrEP is not 100% effective and will not prevent the acquisition of HIV strains resistant to FTC and TDF.

Cost effectiveness

As cost has been a barrier identified by both providers and patients, the price of daily FTC/TDF as a prevention intervention should be evaluated and weighed against its effectiveness. The cost effectiveness of PrEP administration was investigated by modeling HIV incidence in MSM aged 15 to 65 years old residing in Los Angeles County.⁵⁸ Incidence data were evaluated to estimate discounted costs, quality-adjusted life-years (QALYs), and incremental cost effectiveness ratios of various HIV prevention strategies. The model estimated a cumulative HIV incidence of 99,874 cases of HIV without PrEP, whereas PrEP implementation would avoid 58,881 (59%) new infections. The combination of FTC/TDF for PrEP was found to be highly cost effective relative to treating new HIV infections with ART at just \$27,863/QALY and compared to a US willingness-to-pay threshold of \$150,000/QALY. Of note, cost effectiveness in this particular model was dependent upon full adherence to PrEP and high PrEP initiation rates among MSM in this population.

Another cost-effectiveness study modeled HIV incidence in all MSM aged 13 to 64 years in the United States and analyzed QALYs and health care costs of PrEP over a 20-year time period.⁵⁹ Without PrEP initiation, the study estimated 491,784 HIV infections would occur, but if 20% of the MSM population initiated PrEP, then the incidence rate would decrease by 62,759 new HIV infections over 20 years, which correlates with an incremental cost of \$95 billion in the total cost of PrEP, or \$2 million per HIV infection prevented, compared to the cost of treating HIV. However, if high-risk MSM were exclusively targeted, then the total health care incremental cost would be \$75.5 billion, or \$600,000 per HIV infection prevented. PrEP is a costly means of prophylaxis, however it was shown to be a cost-effective solution in preventing HIV infection in this model, particularly when targeted at high-risk MSM.

Similarly, a study modeled cost effectiveness of 25% PrEP coverage in people who inject drugs.⁶⁰ This study found that although random enrollment was not considered cost-effective, targeting enrollment to (i) partners, (ii) individuals with the highest number of sexual and needle partners, or (iii) individuals with sexual and needle-sharing partners with known HIV positivity were all cost effective with the latter scenario being the most cost effective, further supporting a targeted approach to PrEP rollout.

When the role of drug resistance was factored into PrEP cost effectiveness, it was found that expanding PrEP to medium coverage of 50% in San Francisco would prevent 13,798 new HIV infections and cost a total additional \$5,477,000,000 over 20 years.⁶¹ However, keeping PrEP coverage at current rates (38%) and increasing effort of early ART initiation (from 1.6 years to 1.0 years post-diagnosis) would only cost an additional \$207,000,000 making it the most cost-effective method simulated.

Drug cost to consumers and coverage gaps have particularly impacted access to PrEP. Until recently, the components of FTC/TDF were branded. The patent on TDF expired in December 2017, but FTC remains patented until 2021 potentially limiting the marketing of an FTC/TDF generic combination until that date. Insurance coverage for FTC/TDF for PrEP has increased substantially since its approval for this indication, but regions in the South and youth still have significant coverage gaps.⁶² Availability of generic PrEP in the future will

significantly impact the cost-effectiveness conversation and may aid in closing ongoing coverage gaps.

Role of the Pharmacist in PrEP

There are clear barriers to optimizing the use of PrEP among at-risk individuals; pharmacists may be uniquely positioned to address many of these barriers. The inclusion of pharmacists in medication management has improved adherence in numerous disease states, including HIV.³³ In community settings, pharmacists have access to patient refill data and are typically dispensing prescriptions on a monthly basis. This allows for opportunities to address adherence with greater frequency and with more data than other providers have available. A delay in refilling FTC/TDF can prompt an adherence discussion and ideal adherence can be reinforced to encourage retention over time.

Many at-risk individuals may not be linked to infectious disease physicians or even PCPs. A recent study evaluating the geographic distribution of PrEP clinics found that one in eight of PrEP-eligible MSM have to drive more than 30 minutes to access PrEP.⁶² Community pharmacies may be more accessible. With the growth of collaborative practice agreements in many states, one-stop PrEP clinics in community pharmacies may represent a novel and effective way to increase accessibility to PrEP. At a Seattle community pharmacy PrEP clinic known as One-Step PrEP, PrEP was provided under a collaborative practice agreement to 245 at-risk individuals in 1 year. Retention rates were relatively high (75%) and the clinic was found to be cost-effective, turning a profit within the first year.⁶³ An Iowa program known as TelePrEP utilizes pharmacists to ensure that high-risk individuals in rural areas have access to PrEP by allowing for in-home visits via video conferencing.⁶⁴ A number of community Walgreens pharmacy locations have also expanded clinical services to include PrEP.⁶⁵ Pharmacists can play a significant role in addressing the barriers to PrEP use by providing adherence support and expanding accessibility. Further pharmacist involvement in PrEP could help to address many of the concerns of both patients and providers and ultimately help to expand PrEP access and efficacy for those most at risk of contracting HIV.

Conclusion

Since the 2012 FDA approval of FTC/TDF for PrEP, FTC/TDF has been implemented in various clinical setting throughout the United States, however, only a fraction of patients with an indication for PrEP have been prescribed the medications and barriers to the use of FTC/TDF remain. Increased education to both patients and providers is needed to increase awareness, acceptance, and adherence of PrEP. To date, no significant unexpected medication AEs have been related to PrEP use; however, the long-term toxicities of TDF may reduce enthusiasm for some patients and prescribers. More studies are needed to further understand risk compensation and behavioral changes associated with PrEP use, but current data highlight the importance of patient counseling and that PrEP should not be used in isolation, but as a component of a comprehensive HIV prevention package. Drug resistance has been limited to cases of transmission during low adherence or of transmission of multidrug-resistance virus. Cost effectiveness of PrEP will continue to be a relevant consideration given the increasing pressures on our health care system. Future interventions

for PrEP are being designed that may overcome some of the barriers to use (e.g., long-acting therapies to address adherence and acceptance; alternative agents with higher barrier to developing HIV resistance and/or reduced long-term toxicities). Integration of PrEP with pharmacy services increase accessibility as well as improve adherence and retention. In summary, the studies evaluating the implementation of FTC/TDF as PrEP since its approval for this indication demonstrate potential for decreasing new occurrences of HIV infection when prescribed by informed providers and administered to informed and adherent at-risk patients. Additional studies of PrEP implementation in black MSM, transgender women, heterosexual men and women, and IVDUs are still needed to broaden the available real-world data and further refine best practices.

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Table 1.Summary of Results from iPrEX OLE, ATN 110, and The US PrEP Demonstration Project⁸⁻¹⁰

	iPrEX OLE⁸ (n=1225)	ATN 110⁹ (n=200)	The US PrEP Demonstration Project¹⁰ (n=557)
Population	MSM, transgender women	MSM, 18-22 years	MSM, transgender women
HIV Infections	28 HIV Infections (7 had discontinued PrEP) 1.8/100 py vs. 2.6/100 py without PrEP (HR 0.5, 95% CI 0.3 to 1.0)	4 HIV infections 3.3/100 py	2 HIV infections Incidence 0.4% (95% CI 0.1 to 1.5)
Patient Acceptance	77% accepted PrEP Reasons for nonacceptance: concerns for side effects (50%), pill burden (16%), personal preference (13%), alternative prevention methods (14%), societal stigma (10%)	60% found taking FTC/TDF daily to be acceptable	PrEP was interrupted 86 times for 84 patients (15%) due to side effects, concern for long term effects, and low self-perceived risk
Adherence 4 doses/week by drug concentrations	33% HIV incidence 0.0/100 py with 4 doses/week vs. 4.7/100 py with no drug in DBS (p<0.0001)	34% at 48 weeks 90% had detectable drug concentrations at 12 weeks and 69% had detectable at 48 weeks	63% 2.9% had concentrations consistently correlated to <2 doses/week
Adverse Effects	3 grade 1 increases in SCr	3 grade 3 events (nausea, weight loss, headache) 1 grade 1 increase in SCr Significant decreases in BMD Z-scores in the hip (-0.4%; p<0.001) and whole body (-0.6%; p<0.001)	22 grade 1 and 1 grade 2 increases in SCr
Risk Compensation	Proportion reporting condomless receptive anal intercourse decreased from 34% to 25% with PrEP (p=0.006); drug concentrations were higher in this group (p<0.0001) Syphilis rates comparable on PrEP vs. not on PrEP (7.2 vs. 5.4/100 py; HR 1.4, 95% CI 0.8 to 2.2)	Drug concentrations higher in those reporting recent condomless sex (p=0.01) STI rate 66% (95% CI 51 to 82)	Decreases in mean number of anal intercourse partners (11 to 9.3; p=0.04) and condomless receptive anal intercourse encounters (p=0.007) STI rate 90/100 py (95% CI 81 to 99)
Resistance	1 seroconversion with M184V mutation	No resistance detected; no detectable TFV-DP in the 4 patients who seroconverted	No resistance detected; both seroconversions had TFV-DP concentrations correlated to <2 doses/week

ATN 110 = Adolescent Trials Network 110 Study, BMD = bone mineral density, CI = confidence interval, DBS = dried blood spots, FTC/TDF = emtricitabine-tenofovir disoproxil fumarate, HIV = human immunodeficiency virus, HR = hazard ratio, iPrEX OLE = Uptake of Preexposure Prophylaxis, Sexual Practices, and HIV Incidence in Men and Transgender Women Who Have Sex with Men: A Cohort Study, MSM = men who have sex with men, PrEP = pre-exposure prophylaxis, py=person years, SCr = serum creatinine, STI = sexually transmitted infection, TFV-DP = tenofovir diphosphate

Table 2.Summary of Patient and Provider Acceptance Studies¹¹⁻²⁸

Study	Population	N	Acceptance	Barriers
Patients				
Hoff et al ¹¹	MSM Serodiscordant (HIV+/HIV-) and seroconcordant (HIV-/HIV-) couples	171	57% HIV- men in serodiscordant and 46% HIV- men in seroconcordant relationships indicated PrEP would be a good prevention strategy for themselves	Not reported
Rolle et al ¹²	MSM African American 16-29 years of age	184	64% expressed interest in PrEP 34% were prescribed PrEP 20% initiated PrEP	Of those who did not initiate PrEP, the following reasons were reported: consistent condom use, worried about side effects, lack of social support, and would be unhappy taking a pill every day
Mayer et al ¹³	MSM	4698	17% had used PrEP	22% were unaware of PrEP 85% had never used PrEP due to concerns of cost (40%), side effects (31%), effects in insurance (20%), and not feeling at risk (19%)
Restar et al ¹⁴	Young Transgender Women (16-29 years)	230	66% expressed interest in PrEP when told about it Acceptability of PrEP was associated with PrEP interest and having a medical provider who met health needs	68% were unaware of PrEP Most common reasons for disinterest in PrEP: Concern for side effects (21%) Mistrust of providers and researchers (17%)
Park et al ¹⁵	Women on PrEP Most in known serodiscordant relationships	12	Reported PrEP allowed them to remain healthy, improve intimacy with their partners, and reduce anxiety of potentially being infected with HIV	Most reported PrEP-related stigma and did not disclose PrEP use to others
Koren et al ¹⁶	Women	389	57% willing to take PrEP 64% felt comfortable discussing PrEP with their doctor	73% had never heard of PrEP Concerns of cost (44%) and side effects (39%)
Blumenthal et al ¹⁷	Women	18	Most said they would be interested in initiating PrEP as part of a PrEP demonstration project	Expressed limited knowledge of PrEP Concerns for side effects, resistance, misuse, effects on pregnancy, stigma, and long term effects Identified competing priorities, lack of partner support, and judgement from providers as barriers
Shrestha et al ¹⁸	IVDUs	20	Most would be interested in trying PrEP. Those not interested in PrEP stated that they did not engage in risky behaviors, but would be interested if they did engage in risky behaviors in the future.	95% had never heard of PrEP Concerns of risky behaviors, cost, side effects, drug interactions with methadone, burden of daily medication, and stigma were expressed
Kuo et al ¹⁹	IVDUs and heterosexuals	942	Not reported	87% of heterosexuals had never heard of PrEP <1% had taken PrEP

Study	Population	N	Acceptance	Barriers
Patients				
				91% of IVDUs had never heard of PrEP None had taken PrEP
Providers				
Okoro et al ²⁰	Community pharmacists in Minnesota	347	33% had dispensed	Primary concerns with PrEP implementation were identifying appropriate candidates (20%), patient adherence (16%), and cost (15%) 26% reported they would be comfortable counseling about PrEP; most discomfort was regarding knowledge about medication (32%) and behavior modification (20%)
Shaeer et al ²¹	Florida pharmacists	225	22% had dispensed	47% were uncomfortable counseling about PrEP and 71% felt they did not have sufficient knowledge about PrEP to counsel
Unni et al ²²	Community pharmacists in Utah	251	Not reported	Actual knowledge of PrEP was higher than self-perceived knowledge. 20% agreed they were capable of counseling about PrEP; was correlated with education level (PharmD vs Bachelor) and years of experience
Karris et al ²³	Infectious Diseases Physicians	573	9% had prescribed	14% reported they would not provide PrEP based on concerns for drug resistance (77%), providing potentially toxic drugs to healthy individuals (53%), and lack of evidence in real-world settings (53%)
Blumenthal et al ²⁴	Physicians, nurse practitioners, nurses, social workers, and medical students attending infectious diseases conferences in New Year, San Diego, and Los Angeles	233 (including 201 prescribers)	21% had prescribed	35% thought HIV providers should prescribe PrEP, 31% non-HIV providers, 21% public health departments (21%), and 10% STI clinics Greater than 40% of participants reported drug toxicities, potential resistance, and adherence issues may limit their willingness to prescribe PrEP
Rapeephan et al ²⁵	Physicians, PA, registered nurses, medical students, medical assistant, research coordinator, PA student at Tufts Medical Center in Boston, MA	80 (including 61 prescribers)	15% had prescribed 75% would refer patients to infectious diseases specialist for PrEP	Prescribers indicated discomfort with prescribing PrEP due to not enough knowledge (73%), lack of experience (56%), and not covered by insurance (18%)
Tortelli et al ²⁶	Emergency physicians at Washington University in St. Louis, MS	88	94% were interested in receiving training on PrEP	24% were knowledgeable of current guidelines 23% were knowledgeable of referral information Major concerns included lack of efficacy (54%), side effects (90%), and resistance (70%)
Zhang et al ²⁷	Local health departments in North Carolina	56	4% had prescribed 7 (13%) had referred patients for PrEP services	The majority of reasons cited by the health departments for not providing PrEP were related to lack of resources and training
Shrestha et al ¹⁸	Infectious diseases nurses, addictions counselors, HIV prevention counselor, physicians,	10	Not reported	Only one had read the CDC guidelines for PrEP use Concerns expressed included, patient acceptability, cost,

Study	Population	N	Acceptance	Barriers
Patients				
	and an administrator treating IVDUs			increase in STIs, adherence, side effects, stigma, and administrative logistics
Petroll et al ²⁸	PCPs and HIV providers (physicians, NPs, and PAs)	525	17% PCPs had prescribed 64% HIV providers had prescribed	28% PCPs felt familiar with PrEP (vs. 76% HIV providers) PCPs identified limited knowledge and concerns about insurance coverage as barriers

CDC = centers for disease control and prevention, HIV = human immunodeficiency virus, IVDUs = Intravenous Drug Users, MSM = men who have sex with men, NP = nurse practitioner, PA = physician assistant, PCP = primary care provider, PrEP = pre-exposure prophylaxis, STI = sexually transmitted infection