Emtricitabine-tenofovir (Truvada)

Abbreviated Review for Pre-Exposure Prophylaxis of HIV

May 2013

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- In July 2012, the FDA approved the use emtricitabine-tenofovir (FTC-TDF) as pre-exposure prophylaxis (PrEP) for the prevention of HIV in combination with safer sex practices in sexually-active adults at high risk of acquiring HIV through sexual transmission.
- The recommended dose for the prevention of HIV is emtricitabine 200 mg with tenofovir 300 mg once daily. Renal dose adjustments are not required as the use of FTC-TDF for PrEP in HIV-uninfected individuals is not recommended when creatinine clearance (CrCl) is less than 60 mL/min.
- For the FDA approval of this indication, four randomized, controlled trials evaluated the efficacy of FTC-TDF to prevent HIV infections in various populations of high-risk, uninfected individuals in the context of a comprehensive prevention program.
  - Study populations included men who have sex with men (MSM), serodiscordant couples, and high-risk heterosexuals residing in HIV endemic regions, namely sub-Saharan Africa. The mean age of study participants across these trials ranged from 24 to 35 years, and subjects were followed for a median of 1-2 years.
  - Overall, these studies demonstrated significant reductions in the risk for acquiring HIV in subjects receiving FTC-TDF compared to placebo. The futility of the FEM-PrEP trial was primarily attributed to non-adherence.
  - In uninfected individuals, FTC-TDF was not associated with an increase in serious adverse events or laboratory abnormalities compared to placebo over a span of roughly two years of follow-up.
  - Subsequent to FDA approval, preliminary results from the VOICE trial demonstrated no difference in the risk of acquiring HIV with FTC-TDF compared to placebo. Low adherence to study products may have contributed to lack of efficacy, but definitive conclusions are pending the published results of the trial.
- FTC-TDF is contraindicated for PrEP in persons with unknown or positive HIV-1 status and should only be used in combination with other antiretroviral agents in HIV-infected individuals.
- FTC-TDF should only be used in patients confirmed to be HIV-negative since resistance mutations may emerge in individuals with undetected HIV-1 infections because FTC-TDF alone do not comprise a complete treatment regimen for HIV-infected individuals.
- Since FTC-TDF is not completely effective in preventing HIV and other sexually transmitted diseases, PrEP should be initiated in conjunction with other preventative measures, including the proper use of condoms, counseling on the reduction of high-risk behaviors, and the importance of strict adherence. HIV testing should occur every three months in patients receiving FTC-TDF for prevention of HIV and screening for sexually transmitted infections should occur at least yearly.
- PrEP has the potential to contribute to the safe and effective prevention of HIV if targeted to appropriately selected high-risk sexually active adults. Its efficacy is highly dependent on adherence to daily doses of medications and if prescribed should be delivered as part of a comprehensive regimen of preventative services including condoms and routine HIV screening.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating emtricitabine-tenofovir for pre-exposure prophylaxis of HIV (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

The pharmacology and pharmacokinetics of FTC-TDF has previously been evaluated in HIV-infected individuals. Relevant data for PrEP, specifically regarding penetration into relevant tissues, are reviewed below.

Both emtricitabine and tenofovir exhibit long plasma half-lives with even longer intracellular half-lives. Emtricitabine and tenofovir distribute and accumulate in relevant tissues within 2 hours of the first dose and remain above plasma levels for most of the dosing interval.[1,2]

Table 1. Pharmacokinetics of emtricitabine and tenofovir in plasma and target tissues[1]

Parameter	Emtricitabine	Tenofovir
Concentration at 24 hours*		
Blood plasma	47	41
Seminal plasma	253	23
Cervicovaginal fluid	1183	69
Rectal tissue	124	1877
Vaginal tissue	63.4	6.8
Cervical tissue	170	50
Half-life (days)		
Plasma	0.6	0.5
Intracellular**	4.8	6.25

* Plasma and fluid: ng/mL; tissue: ng/g
** Phosphorylated analogues

FDA Approved Indication(s)

Emtricitabine-tenofovir is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk.[3]

The CDC is leading national efforts to develop comprehensive Public Health Service guidelines for PrEP. Until those more detailed guidelines are available, the CDC have published interim guidance on the use of emtricitabine-tenofovir for PrEP in high-risk men who have sex with men (MSM) and heterosexually active adults available at the following links:[4,5]

- Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm)
- Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a2.htm)

Current VA National Formulary Alternatives

No other antiretrovirals are currently approved for the prevention of HIV infection.

Dosage and Administration

The recommended dose for the prevention of HIV is emtricitabine 200 mg coformulated with tenofovir 300 mg once daily. Renal dose adjustments are not required as the use of FTC-TDF for PrEP in HIV-uninfected individuals is not recommended when CrCl $\leq$ 60 mL/min.[3]

Efficacy

The efficacy of FTC-TDF was evaluated in four phase III, randomized, placebo-controlled trials in various populations of high-risk, HIV-uninfected individuals. However, three of these studies were solely conducted in sub-Saharan Africa while the fourth study enrolled roughly 200 (10%) subjects from the United States. The results of all four trials were published in the New England Journal of Medicine.

Patients included in these trials were young healthy subjects with adequate renal function (defined as CrCl $\geq$ 60 mL/min) and hepatic function (defined as liver transaminases $\leq$ 3 times the upper limit of normal). Exclusion criteria included receipt of other antiretroviral agents or concomitant nephrotoxic agents and any significant comorbidities requiring medical therapy. Furthermore, all four study protocols required participation in comprehensive prevention programs at monthly follow-up visits as adjunct interventions.[6-9]

The primary efficacy endpoint across all four studies was the rates of HIV-1 seroconversion. This was measured in both the per-protocol (PP) and modified intent-to-treat (mITT) populations. The mITT population excluded any patients that

were subsequently found to have been HIV-positive at enrollment. Secondary outcomes included rates of adherence, risk compensation, and effect on early HIV-1 disease.[6-9]

Summary of efficacy findings

- In three of the phase III trials, FTC-TDF was found to significantly reduce the risk of HIV seroconversion in high-risk HIV-uninfected individuals (Table 2). Efficacy of FTC-TDF was strongly correlated with adherence and detectable drug concentrations. Seroconverters had lower adherence rates and lower concentrations of emtricitabine and tenofovir compared with non-seroconverters.[6-9]
- The FEM-PrEP study was terminated due to futility which was partially attributed to lower rates of detectable drug concentrations despite high levels of self-reported adherence (Table 3).[5]
- The impact of PrEP with daily FTC-TDF on risk-taking behavior was stable or decreased in all four trials. The major risk-taking behaviors analyzed were rates of unprotected intercourse and number of sexual partners.
- Resistance in subjects that seroconverted after enrollment was not detected over roughly 2 years of follow-up. However, resistance mutations were detected in subjects that were later found to be HIV-positive at or before enrollment.[6-9]

Table 2. Summary of efficacy in published clinical trials evaluating the use of FTC-TDF for PrEP[6-9]

Trial	Population	RR (95% CI)	ARR
iPrEx	MSM (N=2499)	44% (15, 63)	2.2%
Partners-PrEP	Serodiscordant couples (N=4758)	75% (55, 87)	2.5%
TDF2	High-risk heterosexuals (N=1219)	62% (22, 83)	2.4%
FEM-PrEP	High-risk females (N=2120)	6% (-52, 41)	0.2%

RR = relative risk reduction; ARR = absolute risk reduction; CI = confidence interval; MSM = men who have sex with men

Table 3. Impact of adherence and detectable drug concentrations on effectiveness in clinical PrEP trials[6-9]

Trial	Adherence estimates (%)	Detectable drug concentrations (%)		
		Seroconverters	Non-seroconverters	RR
iPrEx	95*	9	51	92%
Partners-PrEP	92**	31	82	90%
TDF2	84**	50	88	--
FEM-PrEP***	95*	26	35	--

* Self-reported adherence; ** Calculated based on pill counts; ***Target TDF concentration = 10 ng/mL in the FEM-PrEP study; RR = risk reduction

For further details on the efficacy results of the published clinical trials, refer to *Appendix: Clinical Trials* (page 7).

The VOICE trial enrolled 5029 heterosexual females from South Africa, Uganda, and Zimbabwe and assessed the safety and efficacy of 1% vaginal tenofovir gel, oral TDF, and oral FTC-TDF.[10] The mean age of female subjects was 25.3 years, and the majority of women (79%) were unmarried. Approximately 20% of subjects reported greater than two male partners within the prior three months. Preliminary results revealed no difference in risk reduction between FTC-TDF and placebo (hazards ratio [HR] = 1.04; 95% confidence interval [CI], 0.73-1.49; P > 0.2). The vaginal tenofovir gel and oral TDF arms also showed no difference in risk of acquiring HIV compared to placebo. In a subgroup analysis, serum or vaginal drug concentrations were detected in 28% of participants randomized to TDF, 29% to FTC-TDF, and 22% to tenofovir gel. Predictors of detectable concentrations were being married and age >25 years. Incidence of HIV in young, unmarried women was 8.8% compared to 0.8% in older, married women.[11] Detectable drug concentrations were present in 21% and 54% of women in these groups, respectively.

Adverse Events (Safety Data)

Two initial phase II safety studies of PrEP with MSM in the US and female sex workers in sub-Saharan Africa revealed no short-term differences in the rates of adverse events over a span of one year in subjects taking oral TDF and placebo.[12,13] Safety data from the published clinical trials and the VOICE study showed similar safety outcomes. The adverse events reported more commonly with FTC-TDF compared with placebo in the PrEP trials were nausea, vomiting, and diarrhea. Rates of other adverse events and discontinuation due to safety concerns were similar compared to placebo. Follow-up in these studies spanned roughly 2 years and longer-term safety data in HIV-uninfected individuals have not yet been determined.[6-9]

In iPrEx, there was a small but statistically significant decrease in creatinine clearance associated with TDF compared with placebo (-2.4 mL/min versus -1.1 mL.min; P = 0.02).[14] Also, in TDF2, bone mineral density scores were significantly

lower in the FTC-TDF arm, but these differences were small and of unknown clinical significance. Fractures after initiation of study treatment occurred in 7 and 6 patients in the FTC-TDF and placebo groups, respectively (P = 0.74).

The rates of laboratory abnormalities listed in Table 4 include any changes in laboratory function tests. Rates of serious abnormalities (defined as Grade 3 or higher) were less than 1-2%.[6-9]

Table 4. Summary of adverse events with FTC-TDF in published PrEP trials[6-9]

Trial	Elevated SCr (%)	Elevated ALT (%)	Elevated AST (%)	Bone fracture (%)
iPrEx*	2	14	17	<1
Partners-PrEP*	1	2	2	<1
TDF2*	<1	5	6	1
FEM-PrEP*	6	12	18	--

SCr = serum creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase
* All values not statistically significant compared with placebo

Deaths and Other Serious Adverse Events

The rates of serious adverse events, including elevated serum creatinine, liver transaminases, and bone fractures, were similar between the active and placebo arms. There were no deaths reported in any of the PrEP trials with daily FTC-TDF.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 7).

Contraindications

FTC-TDF is contraindicated for PrEP in persons with unknown or positive HIV-1 status and should only be used in combination with other antiretroviral agents in HIV-infected individuals.[3]

Warnings and Precautions

The following warnings and precautions are specific to the use of FTC-TDF for the prevention of HIV-1 infection in uninfected individuals:[3-5]

FTC-TDF should not be used if CrCl is less than 60 mL/min. If decreases in CrCl are observed during PrEP, other potential causes should be evaluated and potential risk and benefits of continued use should be re-assessed.

Since FTC-TDF is not always effective in preventing the acquisition of HIV infections, FTC-TDF should be used as a component of a comprehensive prevention strategy that includes other prevention measures, such as the following:[3-5]

- Counsel uninfected persons on safer sex practices, including appropriate regular condom use, knowledge of their HIV status as well as that of their partners, and regular testing for sexually transmitted infections that can facilitate transmission of HIV.
- Inform uninfected persons on their risk-taking behaviors and support their efforts in risk reduction.
- Counsel patients on the importance of strict adherence since the effectiveness of FTC-TDF is strongly correlated with adherence levels as demonstrated by detectable drug concentrations in clinical studies.
- Only use FTC-TDF in patients confirmed to be HIV-negative since resistance mutations may emerge in individuals with undetected HIV-1 infections because FTC-TDF alone do not comprise a complete treatment regimen for HIV-infected individuals. Patients should be screened at least every 3 months during PrEP and discontinued if acute HIV infection is suspected following potential exposure events.
- PrEP should not be started in persons with signs or symptoms of acute viral infections or potential exposure events within the past month. Initiation of FTC-TDF should be delayed for at least 1 month with confirmation of the patient's HIV status.

Special Populations

Pregnancy

The effects of FTC-TDF during chronic fetal exposure could not be adequately assessed because women who became pregnant during the PrEP trials were promptly discontinued from their medication. FTC-TDF is currently rated as pregnancy category B with no evidence of harm to the fetus reported in the Antiretroviral Use in Pregnancy Registry. Since uninfected women who are pregnant are at higher risk for HIV transmission compared to uninfected women who are not pregnant, continuation of FTC-TDF during pregnancy may provide additional protective benefits but these effects have not yet been determined.[3,5]

Nursing mothers

The CDC interim guidance recommends against the use of FTC-TDF for PrEP in women who are breastfeeding.[5]

Hepatitis B Infection

Potential PrEP candidates should be screened for hepatitis B infection prior to initiating FTC-TDF and vaccinated if susceptible of hepatitis B. If active hepatitis B is diagnosed, consider using FTC-TDF as both treatment for hepatitis B and prevention of HIV infection. Regardless of the decision to initiate PrEP, treatment should be initiated for active hepatitis B infection.[4,5]

Sentinel Events

Adverse drug event reports to the VA Adverse Drug Event Reporting System (VA ADERS) were reviewed for all reports (March 2006 to October 2012) related to sentinel events with FTC, FTC-TDF, and TDF. No sentinel events were reported during this time period.

Drug Interactions

No additional drug interaction studies have evaluated FTC-TDF or the separate components in the prevention of HIV-1 infections, but caution should be exercised when given concurrently with other nephrotoxic agents since those patients were excluded from the clinical studies.[3]

Acquisition Costs

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

Three cost-effectiveness analyses were conducted to evaluate the financial impact of implementing PrEP in MSM within the United States. These models included fixed assumptions, including costs of PrEP, medical screening and monitoring, and cost of treatment in HIV-infected individuals. Varying assumptions included percentage of persons receiving PrEP, level of adherence, and degree of risk compensation.[15-17]

Based on these inputs, the base-case scenarios projected that PrEP would reduce new HIV infections of roughly 10% but with significant variations in cost per quality-adjusted life year gained. The lowest costs per quality-adjusted life year were observed in scenarios in which PrEP was only implemented in high-risk MSM (e.g., average of 5 annual partners).[15-17]

Some of these analyses were limited by their assumptions based on preliminary data from the PrEP studies prior to completion. Additionally, they did not account for the development of resistance and secondary transmission of HIV.[15-17]

Table 5: Summary of base-case scenarios of cost-effectiveness models of PrEP in MSM in the United States[15-17]

	Desai et al. (2008)	Paltiel et al. (2009)	Juusola et al. (2012)
Population	High-risk MSM	MSM, 24-44 years	MSM, 13-64 years
Assumptions			
Annual incidence (%)	1.35	1.6	0.8
Use of PrEP (%)	25	--	20
Efficacy (%)	50	50	44
Adherence	50	Incorporated in efficacy	Incorporated in efficacy
Behaviors	Up to 20% more partners	Incorporated in efficacy	No change
Monthly cost of PrEP ($)	930	724	776
ICER per QALY gained ($)	31,972	298,000	172,091

MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years

Conclusions

PrEP has the potential to contribute to the safe and effective prevention of HIV if targeted to high-risk sexually active adults including MSM and serodiscordant couples. Its efficacy is highly dependent on adherence to daily doses of medications and if prescribed should be delivered as part of a comprehensive regimen of preventative services including condoms and regular HIV follow-up testing.

References

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2. Anderson PL, Kiser JJ, Gardner EM, et al. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *J Antimicrob Chemother* 2011; 66: 240-50
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6. Grant RM, Lama RJ, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; 363 (27): 2587-99.
7. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; 367 (5): 399-410
8. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012; 367 (5): 423-34
9. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; 367 (5): 411-22
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17. Juusola JL, Brandeau ML, Owens DK, et al. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012; 156: 541-50

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Appendix: Clinical Trials

<table>
<tr><td>Citation</td><td>Grant RM, Lama RJ, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010; 363 (27): 2587-99.</td></tr>
<tr><td>Study Goals</td><td>To evaluate the safety and efficacy of once-daily oral FTC-TDF as compared with placebo for the prevention of HIV acquisition among men and transgender men who have sex with men</td></tr>
<tr><td>Interventions</td><td>• Emtricitabine 300 mg and tenofovir 200 mg OR placebo once daily</td></tr>
<tr><td>Methods</td><td>• Study design
○ Prospective, randomized, multinational, placebo-controlled, event-driven trial
○ 11 sites in 9 cities in Peru, Ecuador, South Africa, Brazil, Thailand, and the US
○ Study visits every 4 weeks
▪ Pill counts, adherence counseling, and testing for HIV antibodies
▪ Prevention package – HIV testing, condoms, risk-reduction counseling, and screening and treatment of sexually transmitted infections (STIs)
○ All subjects continued on study drug until last participant completed 48 weeks of follow-up; maximum duration of study participation = 168 weeks
○ Prespecified subgroup analysis to correlate drug concentrations with protective effect
• Efficacy analysis
○ Primary endpoint: incidence of HIV seroconversion
○ Secondary endpoints:
▪ Proportion of and estimated missed doses
▪ Plasma HIV RNA, CD4 cell counts, drug resistance among seroconverters
▪ Hepatic flares in subjects who developed acute hepatitis B infection (HBV) after enrollment
▪ Number of sexual partners and partners with positive or unknown status
○ Safety endpoints:
▪ Grade 1 or higher creatinine toxicity
▪ Grade 3 or higher phosphorous toxicity
▪ Grade 2 or higher clinical or laboratory adverse events (AEs)
• Data analysis
○ 85 incident HIV infections would yield ≥ 80% with a one-sided alpha level of 0.05 to reject a null hypothesis of efficacy of 30% if true efficacy were ≥ 60%</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
○ Subjects who were males at birth and ≥ 18 years
○ HIV-seronegative with evidence of high risk for acquiring HIV
○ Creatinine clearance (CrCl) ≥ 60 mL/min estimated by Cockcroft Gault
○ Hepatic function tests ≤ 2 x upper limit of normal (ULN)
• Exclusion criteria
○ Previously diagnosed active and serious infections (including tuberculosis, all infections requiring parenteral antibiotics, and active hepatitis B infection)
○ Active clinically significant medical problems (including cardiac, pulmonary, endocrine, or malignant disease requiring treatment)
○ Receipt of other antiretroviral therapy, anti-HIV vaccine, or nephrotoxic agents</td></tr>
<tr><td>Results</td><td>• Baseline demographics
○ 2499 subjects enrolled from July 2007 to December 2009
○ Baseline characteristics similar between both groups
▪ All male subjects at birth – 29 reported current gender as female
▪ Most patients enrolled in Peru (56%), Ecuador (12%), and Argentina (12%) with 9% enrolled in the United States
○ Median duration of follow-up = 1.2 years (maximum = 2.8 years)

<table>
<tr><th>Characteristics</th><th>FTC-TDF N=1251</th><th>Placebo N=1248</th></tr>
<tr><td>Mean age (years)</td><td>27</td><td>27</td></tr>
<tr><td>Completed at least secondary school (%)</td><td>76</td><td>80</td></tr>
<tr><td>Circumsized (%)</td><td>13</td><td>14</td></tr>
<tr><td>Race and ethnicity</td><td></td><td></td></tr>
<tr><td>White (%)</td><td>18</td><td>17</td></tr>
<tr><td>Mixed race/other (%)</td><td>67</td><td>69</td></tr>
<tr><td>Hispanic (%)</td><td>72</td><td>73</td></tr>
<tr><td>Risk behaviors</td><td></td><td></td></tr>
<tr><td>Mean number of male partners in last 12 weeks</td><td>18</td><td>18</td></tr>
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URAI with HIV+/unknown status partner (%)	79	81
Transactional sex in last 6 months (%)	41	41
STIs		
HSV-2 seropositivity (%)	37	35
Syphilis (%)	13	13
Hepatitis B status		
Susceptible	66	64
Immune	32	33
Chronic	1	1

- **Primary and secondary efficacy analysis**

Endpoints	FTC-TDF N=1251	Placebo N=1248	HR (95% CI)
HIV seroconversion (no.)	36	64	0.56 (0.37, 0.85)
≥ 50% pill use	23	47	0.50 (0.30, 0.82)
< 50% pill use	13	17	0.68 (0.33, 1.41)
Median time to conversion (days)	35	35	--
HIV RNA (log_{10} copies/mL)	5.15	5.10	--
CD4 count (cells/mm^3)	500	500	--
Resistance in seroconverters (%)	0	0	--
Detectable drug concentrations (no.)	3	0	--
Overall self-reported pill use (%)	95	95	--

  - All HBV infections resolved with detectable immunity by end of study
  - No difference in sexual practices including number of sexual partners, percentage of receptive anal intercourse, and reported condom use
  - Detectable blood concentrations 95% concordant with protective effects – adjusted relative risk reduction = 92% (95% CI, 40-99; p<0.001)

- **Safety analysis**

Outcome	FTC-TDF	Placebo	P value
Any adverse event, no. (%)	867 (69)	877 (70)	NS
Any Grade 3 or 4 adverse event	151 (12)	164 (13)	NS
Elevated creatinine	25 (2)	14 (1)	NS
Bone fracture	15 (1)	11 (<1)	NS
Discontinuation	104 (8)	99 (8)	NS

Authors' Conclusions

- Once-daily oral FTC-TDF provided 44% relative risk reduction from acquiring HIV in high risk men who have sex with men in conjunction with a comprehensive package of prevention services
- High concordance between positive plasma drug detection and seroconversion
- Daily FTC-TDF is not associated with increased moderate or severe adverse effects

<table>
<tr><td>Citation</td><td>Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012; 367 (5): 399-410</td></tr>
<tr><td>Study Goals</td><td>To compare the safety and efficacy of daily oral TDF or FTC-TDF with placebo for pre-exposure prophylaxis against HIV-1 acquisition among heterosexual men and women in HIV-1-serodiscordant partnerships</td></tr>
<tr><td>Interventions</td><td>• Tenofovir 300 mg OR emtricitabine 200 mg with tenofovir 300 mg OR placebo daily</td></tr>
<tr><td>Methods</td><td>• Study design
o Prospective, randomized, multisite, double-blind, placebo-controlled trial
o 9 sites in Kenya and Uganda
o Seronegative and seropositive subjects followed monthly and quarterly, respectively
▪ Provision and collection of study medications and standard laboratory testing including pregnancy (medications held for duration of pregnancy)
▪ Provided HIV-1 primary care services with counseling to initiate antiretroviral therapy (ART) according to national guidelines
▪ Comprehensive prevention package: HIV-1 testing and counseling; risk-reduction counseling, screening and treatment for STIs, and free condoms
• Efficacy analysis
o Primary endpoints: incidence of HIV-1-seroconversion and adverse events (AEs) among HIV-1 uninfected individuals
o Secondary endpoints
▪ Factors influencing efficacy: exposure, gender, and other prevention strategies
▪ Adherence: adherence rates and impact on efficacy and drug concentration testing
▪ Risk compensation: characterize initial and change in sexual behaviors
• Data analysis
o 147 incident HIV infections to provide 80% power with one-sided alpha level of 0.025 to reject a null hypothesis of efficacy of 30% if true efficacy were $\geq$ 60%
o Sample size ~4700 couples with 24-36 months of follow-up and expected incidence of 2.75 per 100 person-years in placebo group</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
o Sexually active couples with plans to remain in the relationship for study period
▪ Seronegative subjects $\geq$ 18 and $\leq$ 65 years, HIV-1 uninfected, and hepatitis B negative with CrCl $\geq$ 60 mL/min and LFTs $\leq$ 2 x ULN
▪ Seropositive subjects $\geq$ 18 years, HIV-1 infected, with CD4 $\geq$ 250 cells/mm^3 and no history of AIDS-defining diagnoses
• Exclusion criteria
o Seronegative subjects
▪ Pregnant or breastfeeding
▪ Previously diagnosed active and serious infections (including tuberculosis, all infections requiring parenteral antibiotics, and active hepatitis B infection)
▪ Active clinically significant medical problems (including cardiac, pulmonary, endocrine, or malignant disease requiring treatment)
▪ Receipt of other ART, anti-HIV vaccine, or nephrotoxic agents
o Seropositive subjects – current use of ART</td></tr>
<tr><td>Results</td><td>• Baseline demographics
o 4758 couples enrolled between July 2008 and November 2010
o Baseline characteristics were balanced between groups including age, gender, education, circumcision status, and baseline risk behaviors
o Total follow-up = 7830 person-years (median = 23 months, range 1-36 months)
o Study drug interruption for safety accounted for less than 1% of follow-up time
<table>
<tr><th>Characteristics</th><th>TDF (N=1584)</th><th>FTC-TDF (N=1579)</th><th>Placebo (N=1584)</th></tr>
<tr><td>Male (%)</td><td>62</td><td>64</td><td>61</td></tr>
<tr><td>Mean age (years)</td><td>34</td><td>35</td><td>35</td></tr>
<tr><td>Mean education (years)</td><td>7</td><td>7</td><td>7</td></tr>
<tr><td>Sex with nonstudy partner (%)</td><td>10</td><td>8</td><td>7</td></tr>
<tr><td>STIs</td><td></td><td></td><td></td></tr>
<tr><td>HSV-2 seropositivity (%)</td><td>55</td><td>54</td><td>58</td></tr>
<tr><td>Syphilis (%)</td><td>4</td><td>4</td><td>4</td></tr>
<tr><td>Index partner</td><td></td><td></td><td></td></tr>
<tr><td>Mean CD4 count (cells/mm^3)</td><td>551</td><td>561</td><td>550</td></tr>
<tr><td>Median HIV-1 RNA ($\log_{10}$ copies/mL)</td><td>3.9</td><td>3.9</td><td>3.9</td></tr>
<tr><td>Couples characteristics</td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

Married (%)	97	98	98
Mean years living together	9	9	9
Number of sex acts in past month	6	6	6
Unprotected sex in past month (%)	28	26	26

- **Primary and secondary efficacy analysis**

Endpoints	TDF N=1584	FTC-TDF N=1579	Placebo N=1584	HR (95% CI)*
HIV-1 seroconversion (no.)	17	13	52	0.25 (0.13, 0.45)
Male (no.)	9	4	24	0.16 (0.06, 0.46)
Female (no.)	8	9	28	0.34 (0.16, 0.72)
HIV viral load index partner				
< 50,000 copies/mL (no.)	13	9	32	0.28 (0.13, 0.58)
≥ 50,000 copies/mL (no.)	4	4	18	0.23 (0.08, 0.68)
CD4 count of index partner				
250-349 cells/mm^3 (no.)	8	4	10	0.39 (0.12, 1.26)
≥ 350 cells/mm^3 (no.)	9	9	42	0.21 (0.10, 0.44)
Outside sexual partner (%)	30	30	29	--
Reported STIs (%)	6	4	5	--

** FTC-TDF versus placebo*

  - HIV-1-protective effects similar across gender, viral load, and CD4 count
  - No difference in initiation of ART in seropositive partners (~21%) and outcomes
  - No resistance mechanisms detected in subjects infected after randomization
  - Overall adherence to study medication = 92%
  - Unprotected sex decreased from 27% to 13% at 12 months and 9% at 24 months
  - Detectable concentration of TDF – RR reduction = 86% with TDF and 90% with FTC-TDF

- **Safety analysis**

Adverse event	TDF	FTC-TDF	Placebo	P Value*
Any grade 3 or 4 event (%)	20	21	19	NS
Elevated creatinine (%)	1	1	1	NS
Bone fracture (%)	<1	<1	<1	NS
Neutropenia (%)	15	18	13	<0.001

** FTC-TDF versus placebo*

Authors' Conclusions	• PrEP with TDF or FTC-TDF reduces HIV-1 acquisition in serodiscordant heterosexual populations but efficacy and development of resistance highly dependent on adherence • PrEP may offer substantial protection against HIV-1 transmission from partners of unknown status or HIV-positive partners not yet initiated on ART

<table>
<tr><td>Citation</td><td>Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med 2012; 367 (5): 423-34</td></tr>
<tr><td>Study Goals</td><td>To evaluate the safety and efficacy of daily oral FTC-TDF in the prevention of HIV infection among sexually active homosexual adults</td></tr>
<tr><td>Interventions</td><td>• Emtricitabine 300 mg with tenofovir 200 mg OR placebo once daily</td></tr>
<tr><td>Methods</td><td>• Study design
o Prospective, randomized, double-blind, placebo-controlled trial
o 2 cities in Botswana
o Monthly follow-up visits
▪ Pill counts, adherence counseling, and testing for HIV antibodies
▪ Prevention package – HIV testing, condoms, risk-reduction counseling, and screening and treatment of sexually transmitted infections (STIs)
• Efficacy analysis
o Primary endpoint: rates of HIV-1 seroconversion
o Secondary endpoints:
▪ Medication adherence and changes in sexual behavior and condom use
▪ Virologic and immunologic response to HIV exposure and seroconversion
o Safety analysis: frequency of Grade 3 or 4 renal or hepatic toxicities, frequency of adverse clinical events, and percent change in bone mineral density (BMD)
• Data analysis
o Sample size of 1000 participants if annual incidence of HIV infection = 5% provides 80% power to reduce the rate of HIV infection by ≥ 65%</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
o Age 18-39 years and sexually active
o HIV-seronegative and hepatitis B negative
o Willing to use effective contraception if female
o Comprehension test score of ≥ 80% after completion of education program
• Exclusion criteria
o Pregnant or breastfeeding if female
o Chronic illnesses requiring ongoing prescription medication
o History of significant renal or bone disease</td></tr>
<tr><td>Results</td><td>• Baseline demographics
o 1219 randomized between February 2007 and October 2009
▪ 1070 patients completed study exit procedures
▪ 397 patients did not complete follow-up with similar rates in both groups
o Total follow-up = 1563 person-years (median, 1.1 years; maximum, 3.7 years)
<table>
<tr><th>Characteristics</th><th>FTC-TDF N=611</th><th>Placebo N=608</th><th>P Value</th></tr>
<tr><td>Male (%)</td><td>46</td><td>46</td><td>0.93</td></tr>
<tr><td>Age</td><td></td><td></td><td>0.34</td></tr>
<tr><td>18-29 years (%)</td><td>92</td><td>90</td><td></td></tr>
<tr><td>30-39 years (%)</td><td>8</td><td>10</td><td></td></tr>
<tr><td>Completed at least secondary school (%)</td><td>97</td><td>97</td><td>1.00</td></tr>
<tr><td>Single (%)</td><td>95</td><td>93</td><td>0.45</td></tr>
<tr><td>Male circumcision (%)</td><td>12</td><td>12</td><td>0.83</td></tr>
<tr><td>Sexual behaviors</td><td></td><td></td><td></td></tr>
<tr><td>Condom use with last partner (%)</td><td>81</td><td>79</td><td>0.66</td></tr>
<tr><td>≥ 5 lifetime partners (%)</td><td>54</td><td>57.9</td><td>0.07</td></tr>
<tr><td>≥ 2 partner in last month (%)</td><td>19</td><td>19</td><td>0.93</td></tr>
<tr><td>HIV-positive partner in last month (%)</td><td>3</td><td>4</td><td>0.85</td></tr>
<tr><td>Sexually transmitted infections</td><td></td><td></td><td></td></tr>
<tr><td>HSV-2 seropositive</td><td>35</td><td>37</td><td>0.11</td></tr>
<tr><td>Syphilis</td><td>1</td><td>2</td><td>0.28</td></tr>
</table>
• Primary and secondary efficacy analysis
<table>
<tr><th>Endpoints</th><th>FTC-TDF N=611</th><th>Placebo N=608</th><th>RR (95% CI)</th></tr>
<tr><td>HIV-1 seroconversion (no.)</td><td>9</td><td>24</td><td>62% (22, 83)</td></tr>
<tr><td>Gender</td><td></td><td></td><td></td></tr>
<tr><td>Male (no.)</td><td>2</td><td>10</td><td>80% (25, 97)</td></tr>
<tr><td>Female (no.)</td><td>7</td><td>14</td><td>49% (-22, 81)</td></tr>
</table></td></tr>
</table>

	Adherence rates (%) 84 84 -- ○ No resistance detected in seroconverters after randomization ○ Decreased reported number of sexual partners with stable condom use but similar between treatment groups ○ Mean drug concentrations lower in seroconverters versus matched non-seroconverters (TDF, 0.3 ng/mL versus 30.6 ng/mL; FTC, 0.5 ng/mL versus 103.3 ng/mL) • **Safety analysis** **Outcome** / **FTC-TDF** / **Placebo** / **P value** Any adverse event, no. (%) 91 88 0.003 Any Grade 3 or 4 adverse event 3 5 NS Elevated creatinine <1 0 NS Bone fracture* 1 1 NS Discontinuation for safety (%) 2 2 NS ** Decreased T and z scores for forearm, hip, and lumbar spine for FTC-TDF (P < 0.01)*
Authors' Conclusions	• Once daily oral FTC-TDF decreased the rate of HIV infection by 62% when combined as part of a comprehensive package of HIV-prevention services • AEs observed in the FTC-TDF group were mostly minor and transient in nature but active subjects had a small but significant decline in BMD over 2 years of prophylaxis • Adherence and careful HIV screening is critical for efficacy and the prevention of the development of resistance

<table>
<tr><td>Citation</td><td>Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med 2012; 367 (5): 411-22</td></tr>
<tr><td>Study Goals</td><td>To assess the effectiveness and safety of FTC-TDF in preventing HIV acquisition</td></tr>
<tr><td>Interventions</td><td>• Emtricitabine 200 mg with tenofovir 300 mg OR placebo daily</td></tr>
<tr><td>Methods</td><td>• Study design
o Prospective, randomized, double-blind, placebo-controlled, multinational trial
o 4 sites in Kenya, South Africa, and Tanzania
o Study terminated early in April 2011 due to lack of efficacy
o Study visits every 4 weeks for up to 60 weeks
▪ Pill counts, adherence counseling, and testing for HIV antibodies
▪ Prevention package – HIV testing, condoms, risk-reduction counseling, and screening and treatment of sexually transmitted infections (STIs)
• Efficacy analysis
o Primary: incidence of HIV-1 and HIV-2 seroconversion
o Secondary:
▪ Early HIV-1 disease: viral load, CD4 count, TDF or FTC resistance
▪ Risk behaviors: number of partners and rates of unprotected sex
o Safety: frequency of adverse events (AEs), Grade 2+ renal toxicity, and Grade 3+ hepatic toxicity
• Data analysis
o N = 3900 to provide 72 infections for power of 90% with one-sided alpha of 0.025 assuming 1-year rate of infection = 3% and relative risk reduction of 70%</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
o HIV-seronegative women between 18-35 years at high risk of becoming infected
o Creatinine clearance (CrCl) ≥ 60 mL/min estimated by Cockcroft Gault
o Hepatic function tests ≤ 2 x upper limit of normal (ULN)
• Exclusion criteria
o Pregnant or breastfeeding or history of significant renal or bone disease
o Previously diagnosed active and serious infections (including tuberculosis, all infections requiring parenteral antibiotics, and active hepatitis B infection)
o Active clinically significant medical problems (including cardiac, pulmonary, endocrine, or malignant disease requiring treatment)
o Active hepatitis B infection
o Receipt of other antiretroviral therapy, anti-HIV vaccine, or nephrotoxic agents</td></tr>
<tr><td>Results</td><td>• Baseline characteristics
o 2120 subjects randomized between June 2009 and April 2011
o Total follow-up = 1407 person-years
▪ 81% and 84% subjects completed study in FTC-TDF and placebo groups
▪ Lost to follow-up mostly due to relocation and unrelated personal reasons
<table>
<tr><th>Characteristics</th><th>FTC-TDF N=1251</th><th>Placebo N=1248</th></tr>
<tr><td>Mean age (years)</td><td>24</td><td>24</td></tr>
<tr><td>Mean education (years)</td><td>10</td><td>10</td></tr>
<tr><td>Married (%)</td><td>30</td><td>32</td></tr>
<tr><td>Primary partner (%)</td><td>99</td><td>99</td></tr>
<tr><td>Other partners (%)</td><td>27</td><td>26</td></tr>
<tr><td>Sexual behaviors (in past week)</td><td></td><td></td></tr>
<tr><td>Sex for money or gifts in past 4 weeks (%)</td><td>13</td><td>12</td></tr>
<tr><td>Mean number of partners</td><td>1</td><td>1</td></tr>
<tr><td>Unprotected sex (no.)</td><td>2</td><td>2</td></tr>
<tr><td>Sexually transmitted infections</td><td></td><td></td></tr>
<tr><td>Syphilis (%)</td><td>2</td><td>1</td></tr>
<tr><td>Chlamydia (%)</td><td>15</td><td>13</td></tr>
<tr><td>Gonorrhea (%)</td><td>6</td><td>5</td></tr>
</table>
• Primary and secondary efficacy analysis
<table>
<tr><th>Endpoints</th><th>FTC-TDF N=1251</th><th>Placebo N=1248</th><th>HR (95% CI)</th></tr>
<tr><td>HIV seroconversion (no.)</td><td>33</td><td>35</td><td>0.94 (0.59, 1.52)</td></tr>
<tr><td>CD4 count (cells/mm^3)</td><td>561</td><td>613</td><td>--</td></tr>
<tr><td>HIV RNA (log_{10} copies/mL)</td><td>5.2</td><td>5.2</td><td>--</td></tr>
<tr><td>TDF resistance (no.)</td><td>0</td><td>0</td><td>--</td></tr>
</table></td></tr>
</table>

	FTC resistance (no.)	4	1	--
	Self-reported adherence rates (%)	95	95	--

- Pill count data consistent with self-reported adherence (~88%)
- Most subjects perceived themselves to be at low risk for HIV infection (~70%)
- Drug-concentration testing (concentration ≥ 10 ng/mL TDF → TDF taken in previous 48 hours)
  - Seroconverters – target plasma concentration detected in ~20% of subjects
  - Non-seroconverters – target plasma concentration detected in ~30% of subjects
- No increased evidence of HIV risk behavior with modest but significant reductions in number of partners and unprotected sex acts

- **Safety analysis**

Outcome	FTC-TDF	Placebo	P value
Any adverse event, no. (%)	74	72	NS
Any serious adverse event	3	2	NS
Elevated creatinine	7	5	NS
Elevated ALT	12	9	NS
Elevated AST	18	15	NS

Authors' Conclusions

- Once daily oral FTC-TDF did not significantly reduce HIV acquisition in women compared with placebo
- Drug-concentration analyses → < 40% of HIV-uninfected women had evidence of recent pill use → trial underpowered to detect effect if low adherence for entire cohort
- Perception of low-risk for HIV infection likely contributed to poor adherence, and high pregnancy rate in women receiving oral contraceptives (incidence rate, 29.0 per 100 person-years) may have indicated difficulty with daily pill regimens