

Findings from a double-blind, randomized, placebo-controlled trial of tenofovir disoproxil fumarate (TDF) for prevention of HIV infection in women

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What is Tenofovir?

- **Nucleotide reverse transcriptase inhibitor used for treatment of HIV-infected individuals**
- **Approved in over 50 countries**
- **Thousands of individuals participated in clinical trials prior to approval**
- **715,000 patient-years of treatment through April 2006**

Study Design and Objective

Expanded Phase 2, multi-center study conducted between June 2004 and March 2006

Study Sites: Douala, Cameroon
Ibadan, Nigeria
Tema, Ghana

Objective: Determine the safety and preliminary effectiveness of a daily dose of 300 mg oral TDF for HIV prevention

Primary Endpoints

Safety Endpoints:

- Liver (AST, ALT) and kidney function (creatinine and phosphorus) testing
- Adverse events (AEs)

Effectiveness Endpoint:

- HIV infection measured by detecting antibodies in oral fluid
- Confirmation by ELISA and/or Western Blot

Key Eligibility Criteria

- HIV antibody negative women
- Willing and able to give informed consent
- 18 to 35 years old
- At risk of HIV infection (≥ 3 coital acts/week and ≥ 4 sexual partners/month)
- Have adequate renal and liver function
 - creatinine <1.5 mg/dL
 - AST and ALT <43 U/L
 - phosphorus ≥ 2.2 mg/dL
- Not be pregnant or breastfeeding

Statistical Summary

- Interim safety analyses at 6 and 12 months
- 90% power to conclude that TDF reduces the rate of HIV infection by at least 50% (if true effectiveness is 83%)
- Assumptions:
 - HIV incidence $\geq 5/100$ person years
 - $>80\%$ retention at 12 months
- Targeted 30 incident infections

Monthly Follow-up Assessments

- Sexual Behavior Questionnaire
- Pre- and post-test HIV counseling
- Pregnancy and HIV tests
- Study drug and condoms
- Safety labs (quarterly)
- Physical exam (quarterly)

Participant Disposition

- **Screened: 2040**
 - 20% did not return for enrollment
 - 17% HIV-antibody reactive
 - 13% laboratory abnormality
 - 8% pregnant
- **Enrolled: 936 women (randomized 1:1 TDF:placebo)**

Participant Demographics

	TDF	Placebo
Mean Age	24	24
Not married/living with a man	93%	89%
≤ 12 Years of school	94%	94%
Prior pregnancy	74%	72%
STI in past 6 months	45%	38%

Baseline Contraceptive Use

	TDF (%)	Placebo (%)
Condom	45	44
None	48	48
Oral	4	5
Injectable	1	1
IUD	0.5	0
Other	0.7	0.9

Self-Reported Sexual Behavior

	Screening	Follow-up
Number of partners (30 days)	21	14
Number of new partners (30 days)	11	6
Number of sex acts (7 days)	12	15
Condom use (last act)	52%	94%

Pregnancy and time off product

- Pregnancy probability was 56 per 100 P-Y
- Impact of pregnancies:
 - Approximately 10% of the total time off product was due to pregnancy

Pregnancy (cont.)

	Theoretical Probabilities			TDF
Days unprotected	1	2	3	
Condom use	90%	90%	85%	94%
Acts per cycle	10	20	20	60
Pregnancy probability	30%	51%	66%	56%

Liver Function Results (on product)

- No significant differences were seen between treatment groups in liver or kidney function
- No participants assigned to TDF had Grade 3+ (>170 U/L) ALT or AST elevations (n=363)
- 2 ALT and 3 AST Grade 3 elevations were seen in the placebo group (n=368)

Frequency of Liver Function Abnormalities (on product)

	Active (%)	Control (%)
Grade 3+ ALT		
West Africa	0	0.9
Viread (907)	4	2
TRUVADA (934)	2	2
Grade 3+ AST		
West Africa	0	1.4
Viread (907)	4	3
TRUVADA (934)	3	2

Kidney Function Results (on product)

- One participant in the TDF group had a Grade 3 decrease in phosphorus (<1.5 mg/dL); spontaneously resolved within 3 months
- No participants had a Grade 2+ creatinine elevation (>2.0 mg/dL)

Liver Function Results (post-product)

- No significant differences were seen between treatment groups in liver function after product withdrawal
 - Including in 56 HBsAg+ (23 TDF; 33 placebo) participants in Ghana
- One participant in Cameroon (who received TDF) had a Grade 3 AST elevation after product withdrawal, which spontaneously resolved within 1 month

Mean LFT Results after Product Withdrawal in Ghana (HBsAg+)

	TDF			Placebo		
	n	ALT	AST	n	ALT	AST
Screening	23	15.6	21.5	33	19.4	21.8
Final pill	23	22	26.7	33	18.9	21.2
Post-product	11	16.9	21.9	16	22.5	24.7

Mean LFT Results after Product Withdrawal in Cameroon

	TDF			Placebo		
	n	ALT	AST	n	ALT	AST
Screening	182	16.5	20.7	189	15.7	18.1
Final pill	170	13.6	16.9	178	13.2	16.3
Post-product	70	18.1	22.8	75	16.1	20.6

Comparison of AEs from the West Africa, Viread (907) and TRUVADA (934) studies

AE	Active (%)			Control (%)		
	WA	907	934	WA	907	934
Headache	13	8	5	12	5	4
Diarrhea	4	16	7	4	10	4
Nausea	5	11	8	4	5	6
Vomiting	1	7	1	1	1	4
Rash	2	7	5	1	4	4

Comparison of AEs from the West Africa and Viread (907) studies

AE	Active (%)		Placebo (%)	
	WA	907	WA	907
Abdominal pain	11	7	10	3
Anorexia	7	4	6	2
Flatulence	5	4	4	1
Asthenia	5	11	6	6

Serious Adverse Events

- 22 SAEs (9 TDF; 13 placebo) in 17 participants
- None considered related to study drug (9 were hospitalizations due to malaria)
- 2 deaths occurred ~ 5 months post product
 1. Unspecified condition with anemia (placebo)
 2. Suspected induced abortion (TDF)

HIV Outcomes

- 8 on-product seroconversions (2 TDF : 6 placebo)
- Incidence Rates:
 - TDF: 0.86 per 100 P-Y
 - Placebo 2.48 per 100 P-Y
- Effect is not statistically significant
 - Rate ratio of 0.35 (95% CI = 0.03-1.93)
- Blood specimens obtained from one of the two participants on TDF showed no evidence of resistance

Conclusions

- **Daily oral use of TDF in HIV-uninfected women was not associated with increased clinical or laboratory adverse events**
- **Effectiveness could not be conclusively evaluated because of the small number of HIV infections observed during the study**
- **Further effectiveness studies should proceed rapidly**