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Tenofovir DF: 48-week final analysis from a phase III, randomized, double-blind, placebo-controlled study in antiretroviral-experienced patients (Study 907)

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Introduction

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate (tenofovir DF) is a nucleotide reverse transcriptase inhibitor (NtRTI) with the following characteristics:

- Single tablet, once-daily dosing
- Activity against wild-type and most nucleoside-resistant HIV
- Activity in resting and activated T cells
- Additive or synergistic activity with other antiretrovirals in vitro

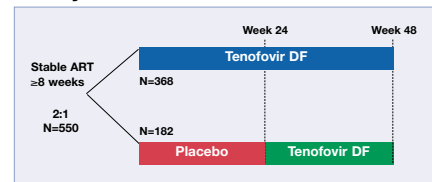
Objective

- To investigate the efficacy and safety of tenofovir DF 300 mg in the treatment of HIV-1 infection

Methods

- The blinded phase of the study was a randomized, double-blind, placebo-controlled study of the safety and efficacy of 300 mg of tenofovir DF administered orally to adult HIV-1-infected patients with plasma HIV RNA levels ≥ 400 copies/mL and $\leq 10,000$ copies/mL. After 24 weeks, all patients received open-label drug through the end of the 48-week study
- At baseline patients were on stable antiretroviral therapy comprising ≤ 4 active agents for ≥ 8 weeks and had adequate renal, hematologic, and hepatic function
- Approximately 50% of patients were randomly assigned to a prospective virology substudy
- At 48 weeks, patients were allowed to rollover into Study GS 99-910, which is a long-term safety study

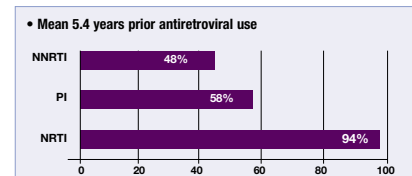
Figure 1 — Study GS 99-907 schema chart



Results

- At baseline, the mean CD4 count was 427 cells/mm³ and the mean plasma HIV-1 RNA viral load was 3.36 log₁₀ copies/mL. Patients enrolled in the study were predominantly male (85%) and Caucasian (69%) with a mean age of 42 years
- Through 24 weeks in both the placebo and tenofovir DF groups, the overall study discontinuation rate and discontinuation rate due to adverse events or intercurrent illness were 6% and 3%, respectively. Through 48 weeks, the study discontinuation rate for the group originally randomized to tenofovir DF was 12%

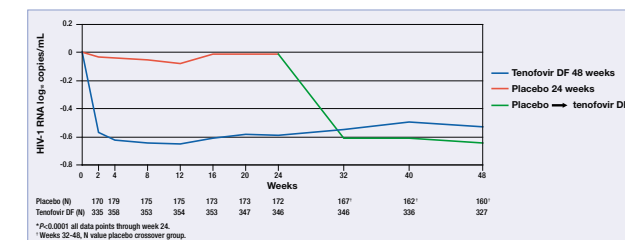
Figure 2 — HIV-1-resistance mutations present at baseline



Efficacy Results

- Through 24 weeks, the tenofovir DF group demonstrated a significant time weighted average change from baseline in HIV-1 RNA log₁₀ copies/mL (DAVG₂₄), the primary endpoint, compared with the placebo group (-0.61 vs -0.03, respectively; $P < 0.0001$)

Figure 3 — Mean change from baseline in plasma HIV-1 RNA*



- Through 24 weeks, the tenofovir DF group demonstrated a significant average increase from baseline in CD4 cell counts in cells/mm³ compared with the placebo group (+12.5 vs -10.8, respectively; $P = 0.0008$)

Figure 4 — Percentage of patients with HIV-1 RNA ≤ 400 and ≤ 50 copies/mL (ITT)

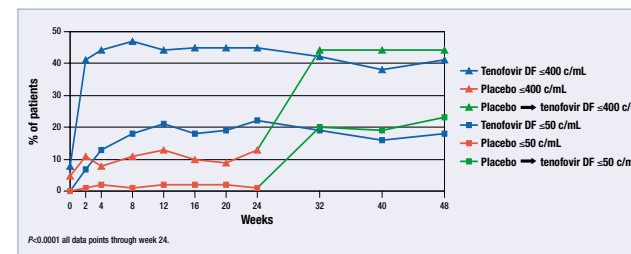


Table 1 — HIV RNA responses by baseline resistance mutations (ITT)

Baseline Mutations	Mean DAVG ₂₄ (N)		P Value	Mean DAVG ₄₈ (N)	
	Tenofovir DF	Placebo		Tenofovir DF	Placebo \rightarrow TDF 24 Weeks
All substudy patients	-0.59 (168)	-0.03 (84)	<0.0001	-0.56 (168)	-0.70 (80)
M184V	-0.68 (117)	-0.05 (54)	<0.0001	-0.64 (117)	-0.81 (51)
TAMs*	-0.47 (114)	+0.03 (61)	<0.0001	-0.45 (114)	-0.57 (58)
NNRTI-R	-0.49 (77)	+0.02 (44)	<0.0001	-0.47 (77)	-0.64 (42)
Protease inhibitor-R	-0.55 (96)	-0.00 (52)	<0.0001	-0.54 (96)	-0.75 (50)

* Thymidine analog mutations are M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N.

Safety Results

Table 2 — Grade 3 or 4 clinical adverse events (occurring in $\geq 2\%$ of patients in any group)

	Tenofovir DF 24 Weeks N=368	Placebo 24 Weeks N=182	Tenofovir DF 48 Weeks N=368	Placebo \rightarrow TDF 24 Weeks N=170
Total number with events	49 (13%)	25 (14%)	73 (20%)	23 (14%)
Diarrhea	3 (<1%)	3 (2%)	5 (1%)	1 (<1%)
Pain	3 (<1%)	1 (<1%)	6 (2%)	1 (<1%)
Depression	1 (<1%)	1 (<1%)	2 (<1%)	3 (2%)

Table 3 — Grade 3 or 4 laboratory abnormalities (occurring in $\geq 2\%$ of patients in any group)

	Tenofovir DF 24 Weeks N=368	Placebo 24 Weeks N=182	Tenofovir DF 48 Weeks N=368	Placebo \rightarrow TDF 24 Weeks N=170
Total number with events	92 (25%)	69 (38%)	128 (35%)	57 (34%)
Hypertriglyceridemia	30 (8%)	24 (13%)	39 (11%)	16 (9%)
Elevated creatine kinase	24 (7%)	26 (14%)	44 (12%)	21 (12%)
Elevated amylase	21 (6%)	13 (7%)	27 (7%)	11 (6%)
Glycosuria	11 (3%)	6 (3%)	12 (3%)	4 (2%)
Elevated AST	10 (3%)	5 (3%)	15 (4%)	9 (5%)
Hyperglycemia	7 (2%)	8 (4%)	10 (3%)	5 (3%)
Elevated ALT	8 (2%)	3 (2%)	14 (4%)	9 (5%)
Neutropenia	2 (<1%)	2 (1%)	6 (2%)	1 (<1%)

Table 4 — Elevation in serum creatinine

	Tenofovir DF 24 Weeks N=368	Placebo 24 Weeks N=182	Tenofovir DF 48 Weeks N=368	Placebo \rightarrow TDF 24 Weeks N=170
Graded Serum Creatinine (mg/dL)				
1 ≥ 0.5 over baseline	6 (2%)	2 (1%)	12 (3%)	6 (4%)
2 2.1-3.0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 3.1-6.0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4 >6.0	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- No patients permanently discontinued the study due to tenofovir DF-related serum creatinine elevations or hypophosphatemia

Conclusions

- Tenofovir DF provided significant reductions in HIV RNA levels in treatment-experienced patients with extensive nucleoside resistance at baseline
- A rapid antiviral response to tenofovir DF was seen at week 2 and maintained through week 48
- Tenofovir DF has a discontinuation rate and safety profile similar to placebo