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Safety profile of tenofovir DF (TDF) in treatment-experienced patients from randomized, placebo-controlled clinical trials

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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 safety of tenofovir DF 300 mg in the treatment of HIV-1 infection

Methods

- Data were pooled from 2 randomized, placebo-controlled studies; a 186-patient Phase 2 study, GS-98-902, and a 550-patient Phase 3 study, GS-99-907
- Patients in both studies added tenofovir DF or placebo to existing background antiretroviral therapy
- The 443-patient "Tenofovir DF 300 mg" group includes all patients in Studies 902 and 907 randomized to tenofovir DF 300 mg and those placebo patients who later received tenofovir DF 300 mg in Study 902
- The 687-patient "All Tenofovir DF" group includes all patients in the "Tenofovir DF 300 mg" group, those placebo patients who later received tenofovir DF 300 mg in Studies 902 and 907, and those patients who initially received 75 mg or 150 mg for 48 weeks in Study 902 who later received tenofovir DF 300 mg

Results

Table 1 – Demographics and baseline HIV disease characteristics

	Placebo (0–24 weeks)	Tenofovir DF 300 mg (0–24 weeks)	All Tenofovir DF (mean=58 weeks)
Number of patients	210	443	687
Mean age (y)	42	41	41
Male	186 (89%)	380 (86%)	598 (87%)
Mean HIV-1 RNA ($\log_{10}$ copies/mL)	3.43	3.40	3.42
Mean CD4 counts (cells/mm^3)	428	411	419

- At baseline, the mean duration of prior antiretroviral use for all patients was approximately 5 years

Table 2 – Grade 3 or 4 adverse events and laboratory abnormalities (occurring in ≥2% of patients in any group)

	Placebo (0–24 weeks)	Tenofovir DF 300 mg (0–24 weeks)	All Tenofovir DF (mean=58 weeks)
Number of patients	210	443	687
Grade 3 or 4 Adverse Events			
Diarrhea	4 (2%)	4 (<1%)	11 (2%)
Depression	2 (<1%)	3 (<1%)	11 (2%)
Grade 3 or 4 Laboratory Abnormalities			
Creatine kinase	30 (14%)	36 (8%)	103 (15%)
Elevated triglycerides	28 (13%)	37 (8%)	89 (13%)
Serum amylase elevation	14 (7%)	21 (5%)	47 (7%)
AST elevation	6 (3%)	16 (4%)	40 (6%)
Urine glucose elevation	6 (3%)	12 (3%)	27 (4%)
Serum glucose elevation	8 (4%)	8 (2%)	24 (3%)
ALT elevation	4 (2%)	10 (2%)	30 (4%)
Neutropenia	3 (1%)	6 (1%)	17 (2%)

- Through 24 weeks, the incidence of study drug discontinuation was similar between the tenofovir DF 300 mg (7%) and placebo (9%) groups. With a mean time on tenofovir DF of 58 weeks, the incidence of study drug discontinuation was 15%
- Few patients discontinued tenofovir DF due to adverse events. Through 24 weeks, the incidence of study drug discontinuation due to adverse events was 3% in both the tenofovir DF 300 mg and placebo groups. With a mean time on tenofovir DF of 58 weeks, the incidence of study drug discontinuation due to adverse events was 6%
- Serious adverse events were infrequent in the Phase 2 and 3 studies and similar incidences of events were reported through 24 weeks for the tenofovir DF (5%) and placebo (8%) groups. With a mean time on tenofovir DF of 58 weeks, the incidence of serious adverse events was 13%

Table 3 – Incidence of elevations in serum creatinine and hypophosphatemia

	Placebo (0–24 weeks)	Tenofovir DF 300 mg (0–24 weeks)	All Tenofovir DF (mean=58 weeks)
Number of patients	210	443	687
Graded Serum Creatinine (mg/dL)			
1 ≥0.5 over baseline	3 (1%)	6 (1%)	32 (5%)
2 2.1–3.0	0 (0%)	0 (0%)	0 (0%)
3 3.1–6.0	0 (0%)	0 (0%)	0 (0%)
4 >6.0	0 (0%)	0 (0%)	0 (0%)
Graded Hypophosphatemia (mg/dL)			
1 2.0–2.2	10 (5%)	27 (6%)	51 (7%)
2 1.5–1.9	5 (2%)	28 (6%)	58 (8%)
3 1.0– 1.4	1 (<1%)	0 (0%)	3 (<1%)
4 <1.0	0 (0%)	1 (<1%)	1 (<1%)

- No patients discontinued study due to tenofovir DF-related serum creatinine elevations or hypophosphatemia
- Serum creatinine elevations and hypophosphatemia were generally transient and resolved with continued tenofovir DF treatment

Table 4 – Incidence of adverse events potentially associated with mitochondrial dysfunction

	Placebo (0–24 weeks)	Tenofovir DF 300 mg (0–24 weeks)	All Tenofovir DF (mean=58 weeks)
Number of patients	210	443	687
Peripheral neuritis	6 (3%)	9 (2%)	37 (5%)
Pancreatitis	2 (<1%)	2 (<1%)	7 (1%)
Lactic acidosis	0 (0%)	1 (<1%)	7 (1%)

- All patients who developed lactic acidosis were also receiving stavudine or didanosine concomitantly.

Conclusions

- During the 24-week placebo-controlled period of the Phase 2 and 3 studies, the safety profile of tenofovir DF was similar to placebo
- The safety profile of tenofovir DF did not significantly change with extended dosing