

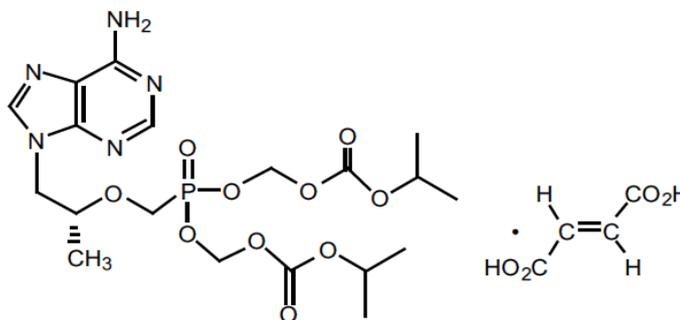
TENOFOVIR APOTEX TABLETS

NAME OF THE MEDICINE

Tenofovir disoproxil fumarate

Chemical Name: 9-[(*R*)-2-[[bis[[isopropoxycarbonyl]oxy]methoxy]-phosphinyl]-methoxy]propyl]adenine fumarate (1:1)

Structural Formula:



Molecular Formula: $C_{23}H_{34}O_{14}N_5P$

Molecular Weight: 635.52

CAS Registry Number: 202138-50-9

DESCRIPTION

Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25°C. The partition coefficient (log P) for tenofovir disoproxil is 1.25 and the pKa is 3.75. The active pharmaceutical product is a single enantiomer that does not undergo racemisation either *in vitro* or *in vivo*.

Each tablet contains 300 mg tenofovir disoproxil fumarate, as the active ingredient. In addition, each tablet contains the following inactive ingredients: lactose, crospovidone, calcium stearate, colloidal anhydrous silica, hypromellose, macrogol 8000, hydroxypropylcellulose, titanium dioxide and indigo carmine aluminium lake.

PHARMACOLOGY

Pharmacological Actions

Mechanism of Action

Tenofovir disoproxil fumarate is a salt of an oral prodrug of tenofovir, a nucleoside monophosphate (nucleotide) analogue and obligate chain terminator with activity against HIV reverse transcriptase and HBV polymerase.

Tenofovir is converted to the active metabolite, tenofovir diphosphate, by constitutively expressed cellular enzymes through two phosphorylation reactions. This conversion occurs in both resting and activated T cells. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ . At concentrations of up to 300 μ M, tenofovir shows no effect on the synthesis of mitochondrial DNA (human liver, skeletal muscle and renal proximal tubular epithelial cells) or lactic acid production (human liver and skeletal muscle cells) *in vitro*.

Pharmacodynamic Effects

Tenofovir has *in vitro* antiviral activity against retroviruses and hepadnaviruses.

Anti-HIV-1 activity in vitro

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC₅₀ (50% inhibitory concentration) for tenofovir was in the range 0.04–8.5 µM. In drug combination studies of tenofovir with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase, and protease inhibitors, additive to synergistic effects were observed. In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Tenofovir shows activity within three fold of wild-type IC₅₀ against recombinant HIV-1 expressing didanosine resistance (L74V), zalcitabine resistance (T69D) or multinucleoside drug resistance (Q151M complex) mutations in reverse transcriptase. Tenofovir shows slightly increased activity against HIV-1 expressing the abacavir/lamivudine resistance mutation M184V. The activity of tenofovir against HIV-1 strains with thymidine analogue-associated mutations (thymidine-associated mutations) appears to depend on the type and number of these resistance mutations. In the presence of mutation T215Y, a twofold increase of the IC₅₀ was observed. In 10 samples which had multiple thymidine-associated mutations (mean 3.4), a mean 3.7-fold increase of the IC₅₀ was observed (range 0.8–8.4). There are insufficient data at this time to correlate specific thymidine-associated mutation patterns with reduced susceptibility to tenofovir.

Multinucleoside resistant HIV-1 with T69S double insertions have reduced susceptibility to tenofovir (IC₅₀ > 10-fold compared with wild type). Tenofovir shows activity against nonnucleoside reverse transcriptase inhibitor resistant HIV-1 with K103N or Y181C mutations. Cross-resistance to protease inhibitor resistance mutations is not expected due to the different viral enzymes targeted.

Strains of HIV-1 with reduced susceptibility to tenofovir have been selected *in vitro*. The selected viruses express a K65R mutation in RT and showed 3 to 4-fold reduced susceptibility to tenofovir. The K65R mutation in RT also results in reduced susceptibility to zalcitabine, didanosine, stavudine (d4T), abacavir and lamivudine (3TC) (14-, 4-, 2-, 3- and 25-fold, respectively). In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. This substitution is also associated with reduced susceptibility to abacavir, didanosine, emtricitabine and lamivudine.

Anti-Hepatitis B Virus Activity in vitro

The *in vitro* antiviral activity of tenofovir against laboratory strains and clinical isolates of HBV was assessed in HepG2 cells. The EC₅₀ values for tenofovir were in the range 0.06–1.5 µM. Tenofovir diphosphate inhibits recombinant HBV polymerase with a K_i (inhibition constant) of 0.18 µM. In *in vitro* drug combination studies of tenofovir with nucleoside anti-HBV reverse transcriptase inhibitors lamivudine, telbivudine and entecavir, additive anti-HBV activity was observed. Additive to slight synergistic effects were observed with the combination of tenofovir and emtricitabine.

Pharmacokinetics

Tenofovir disoproxil fumarate is a water soluble ester prodrug of the active ingredient tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and tenofovir diphosphate. The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Following oral administration, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir in fasted patients was approximately 25%. Following oral administration of a single dose of tenofovir 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. C_{max} and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng•h/mL, respectively.

Administration of tenofovir disoproxil fumarate following a high-fat meal (~700 to 1000 kcal containing 40–50% fat) increases the oral bioavailability, with an increase in tenofovir AUC_{0-∞} of approximately 40% and an increase in C_{max} of approximately 14%. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/mL and 3324 ± 1370 ng•h/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Distribution

After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). *In vitro* protein binding of tenofovir to human plasma or serum protein was less than 0.7% and 7.2%, respectively, over the tenofovir concentration range 0.01–25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (~ 300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1 or CYP1A1/2). Tenofovir disoproxil fumarate at a concentration of 100 µM had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. Based on these data, it is unlikely that clinically significant drug-drug interactions involving tenofovir disoproxil fumarate and medicinal products metabolized by CYP450 would occur.

Excretion

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Linearity/Non-linearity

The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range 75–600 mg and were not affected by repeated dosing at any dose level.

Special Populations

Gender

Pharmacokinetics of tenofovir in patients are similar with regard to gender.

Paediatric Patients 12 Years of Age and Older

Steady-state pharmacokinetics of tenofovir were evaluated in eight HIV-1 infected paediatric patients (12 to < 18 years). Mean (\pm SD) C_{max} and AUC_{0-24} were 0.38 ± 0.13 µg/mL and 3.39 ± 1.22 µg•hr/mL, respectively. Tenofovir exposure achieved in paediatric patients aged 12 years of age and older receiving oral daily doses of tenofovir disoproxil fumarate 300 mg were similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Tenofovir exposure in HBV infected paediatric patients (12 to < 18 years of age) receiving oral daily dose of tenofovir disoproxil fumarate 300 mg tablet was similar to exposures achieved in adults receiving once daily doses of tenofovir disoproxil fumarate 300 mg.

Pharmacokinetic studies have not been performed with in paediatric subjects < 12 years of age.

Elderly Patients

Pharmacokinetic studies have not been performed in the elderly (> 65 years).

Ethnicity

Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal Impairment

The pharmacokinetics of tenofovir are altered in subjects with renal impairment (see **PRECAUTIONS**). In non-HIV and non-HBV infected subjects with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and $AUC_{0-\infty}$ of tenofovir were increased (Table 1). It is required that the dosing interval for tenofovir disoproxil fumarate be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see **DOSAGE AND ADMINISTRATION**).

Table 1: Pharmacokinetic Parameters (Mean ± SD) of Tenofovir¹ in Patients with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)*	> 80 (n = 3)	50–80 (n = 10)	30–49 (n = 8)	12–29 (n = 11)
C _{max} (ng/mL)	335.5 ± 31.8	330.4 ± 61.0	372.1 ± 156.1	601.6 ± 185.3
AUC _{0-∞} (ng·hr/mL)	2184.5 ± 257.4	3063.8 ± 927.0	6008.5 ± 2504.7	15984.7 ± 7223.0
CL/F (mL/min)	1043.7 ± 15.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL _{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

¹ 300 mg, single dose of tenofovir disoproxil fumarate (DF)

* Creatinine clearance calculated using the Cockcroft Gault equation

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate have been studied in non-HIV and non-HBV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

Pharmacokinetic/Pharmacodynamic Relationship

Tenofovir disoproxil fumarate has demonstrated a dose related significant and sustained anti-HIV effect at doses ranging from 75 mg to 300 mg.

Drug Interactions

At concentrations substantially higher (~ 300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9 or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low (see [Metabolism](#), above).

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of tenofovir disoproxil fumarate with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered drug, due to competition for this elimination pathway. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with abacavir, didanosine, efavirenz (EFV), emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin saquinavir/ritonavir and tacrolimus. Tables 2 and 3 summarize pharmacokinetic effects of co-administered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of co-administered drug.

When unboosted atazanavir (400 mg) was co-administered with tenofovir disoproxil fumarate, atazanavir increased tenofovir C_{max} by 14% and AUC by 24%. Similarly, lopinavir (400 mg)/ritonavir (100 mg) increased tenofovir AUC by 32%.

Co-administration of tenofovir disoproxil fumarate with didanosine and atazanavir results in changes in the pharmacokinetics of didanosine and atazanavir that may be of clinical significance. Table 4 summarizes the drug interaction between tenofovir disoproxil fumarate and didanosine. When administered with multiple doses of tenofovir disoproxil fumarate, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (see **PRECAUTIONS**).

Table 2: Drug Interactions – Changes in Pharmacokinetic Parameters for Tenofovir¹ in the Presence of the Co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	n	% Change of Tenofovir Pharmacokinetic Parameters ² (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir	300 once	8	↔	↔	NC
Atazanavir ³	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔
Didanosine (buffered) ⁴	250 or 400 once daily × 7 days	14	↔	↔	↔
Efavirenz	600 once daily × 14 days	29	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Entecavir	1 mg once daily × 10 days	28	↔	↔	↔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↔	↔	↔
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 26 to ↑ 38)	↑ 51 (↑ 32 to ↑ 66)
Methadone ⁵	40-110 once daily × 14 days ⁶	13	↔	↔	↔
Nelfinavir	1250 twice daily × 14 days	29	↔	↔	↔
Oral Contraceptives ⁷	Ethinyl estradiol/Norgestimate Once daily × 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NC
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus ⁸	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔

- Subjects received tenofovir DF 300 mg once daily
- Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
- REYATAZ™ Prescribing Information (Bristol-Myers Squibb)
- Includes 4 subjects weighing < 60 kg receiving ddl 250mg
- R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir DF.
- Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
- Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.
- Subjects received tenofovir DF 300 mg once daily as the combination product tenofovir DF/emtricitabine.

Following multiple dosing to HIV- and HBV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and tenofovir disoproxil fumarate. In a study conducted in healthy volunteers dosed with a single 600 mg dose of ribavirin, no clinically significant drug interactions were observed between tenofovir disoproxil fumarate and ribavirin.

Table 3: Drug Interactions – Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Tenofovir disoproxil fumarate

Co-administered Drug	Dose of Co-administered Drug (mg)	n	% Change of Co-administered Drug Pharmacokinetic Parameters ¹ (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	↔	NA
Atazanavir ²	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir ²	Atazanavir/Ritonavir ³ 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5) ³	↓ 25 (↓ 42 to ↓ 3) ³	↓ 23 (↓ 46 to ↑ 10) ³
Efavirenz	600 once daily × 14 days	30	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily × 10 days	28	↔	↑ 13 (↓ 11 to ↑ 15)	↔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	↔ ↔	↔ ↔	↔ ↔
Methadone ⁴	40-110 once daily × 14 days ⁵	13	↔	↔	↔
Nelfinavir M8 Metabolite	1250 twice daily × 14 days	29	↔ ↔	↔ ↔	↔ ↔
Oral Contraceptives ⁶	Ethinyl estradiol/Norgestimate Once daily × 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Saquinavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29 ⁷ (↑ 12 to ↑ 48)	↑ 47 ⁷ (↑ 23 to ↑ 76)
Ritonavir			↔	↔	↑ 23 (↑ 3 to ↑ 46)
Tacrolimus ⁸	0.05 mg/kg twice daily × 7 days	21	↔	↔	↔

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable
2. REYATAZ™ Prescribing Information (Bristol-Myers Squibb)
3. In HIV infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone (REYATAZ™ March 2004 United States Package Insert)
4. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir DF.
5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.
7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are co-administered.
8. Subjects received tenofovir DF 300 mg once daily as the combination product tenofovir DF/emtricitabine.

Table 4: Drug Interactions – Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir disoproxil fumarate

Didanosine ¹ Dose (mg), Method of Administration ²	Tenofovir DF, Method of Administration ²	n	% Difference (90% CI) vs. Didanosine 400 mg alone, Fasted ³	
			C _{max}	AUC
Buffered tablets				
400 once daily ⁴ × 7 days	Fasted, 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hours after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food 2 hours after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	↔
250 once, fasted	Simultaneously with didanosine	28	↔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

1. See **PRECAUTIONS** regarding use of didanosine with tenofovir DF.
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. Increase = ↑; Decrease = ↓; No Difference = ↔
4. Includes 4 subjects weighing < 60 kg receiving ddl 250 mg.

Intracellular pharmacokinetics

In non-proliferating human peripheral blood mononuclear cells (PBMCs) *in vitro*, the half-life of tenofovir diphosphate was found to be approximately 50 hours, whereas the half-life in phytohaemagglutinin-stimulated PBMCs was found to be approximately 10 hours.

CLINICAL TRIALS

Clinical Efficacy in HIV Infection

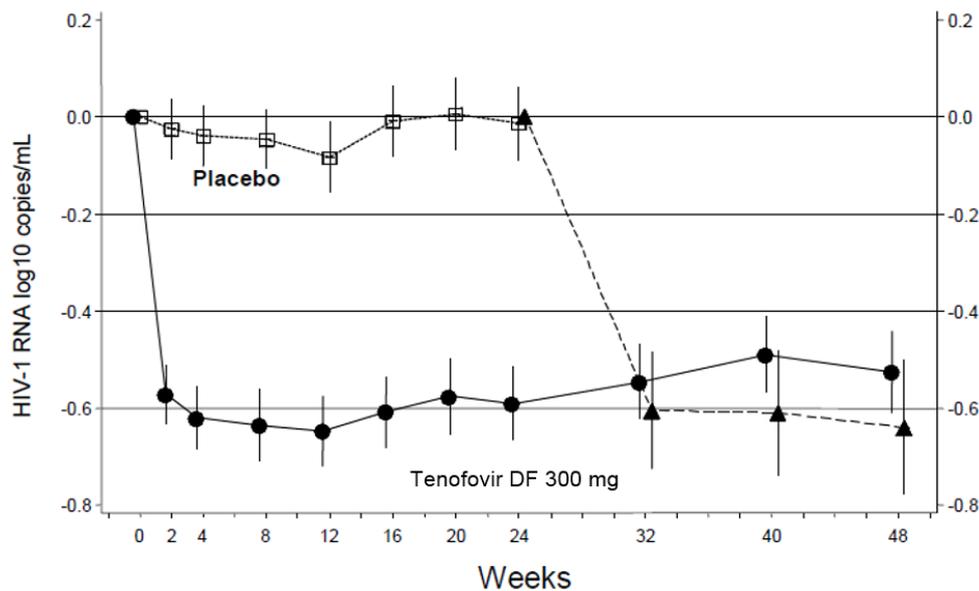
The demonstration of benefit of tenofovir disoproxil fumarate is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of tenofovir disoproxil fumarate in treatment-naïve adults and in treatment-experienced adults.

Treatment-Experienced Adult Patients

Study 907: Tenofovir DF + Standard Background Therapy (SBT) Compared to Placebo + SBT

Study 907 was a 24-week, double-blind, placebo-controlled multicentre study of tenofovir disoproxil fumarate added to a stable background regimen of antiretroviral agents in 550 treatment-experienced patients. After 24 weeks of blinded study treatment, all patients continuing on study were offered open-label tenofovir disoproxil fumarate for an additional 24 weeks. Patients had a mean baseline CD4 cell count of 427 cells/mm³ (range 23–1385), median baseline plasma HIV-1 RNA of 2340 (range 50–75,000) copies/mL and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% Black and 12% Hispanic.

Changes from baseline in log₁₀ copies/mL plasma HIV-1 RNA levels over time up to Week 48 are presented below in Figure 1.

Figure 1: Mean Change from Baseline in Plasma HIV-1 RNA (\log_{10} copies/mL) through Week 48 (Study 907, All Available Data)[†]

◆ Tenofovir DF (n =)	368	335	358	353	354	353	347	346	346	336	327
□ Placebo (n =)	182	170	179	175	175	173	173	172			
▲ Placebo->Tenofovir DF (n =)								170	167	162	160

[†] Patients on placebo after 24 weeks received tenofovir disoproxil fumarate

The percent of patients with HIV-1 RNA < 400 copies/mL and outcomes of patients through 48 weeks are summarized in Table 5.

Table 5: Outcomes of Randomized Treatment (Study 907)

Outcomes	0–24 weeks		0–48 weeks	24–48 weeks
	Tenofovir DF (n = 368) (95% CI)	Placebo (n = 182) (95% CI)	Tenofovir DF (n = 368)	Placebo Crossover to Tenofovir DF (n = 170)
HIV-1 RNA < 400 copies/mL ¹	40% ⁴ (35–45%)	11% ⁴ (6–16%)	28%	30%
Virologic failure ²	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons ³	3%	3%	5%	1%

1. Patients with HIV-1 RNA < 400 copies/mL and no prior study drug discontinuation at Week 24 and 48, respectively.
2. Patients with HIV-1 RNA \geq 400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48, respectively.
3. Includes lost to follow up, patient withdrawal, non-compliance, protocol violation and other reasons.
4. Difference 29% $p < 0.001$.

At 24 weeks of therapy, there was a higher proportion of patients in the tenofovir disoproxil fumarate arm compared to the placebo arm with HIV-1 RNA < 50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4 counts by Week 24 was +11 cells/mm³ for the tenofovir disoproxil fumarate group and -5 cells/mm³ for the placebo group. Mean change in absolute CD4 counts by Week 48 was +4 cells/mm³ for the tenofovir disoproxil fumarate group.

Treatment-Experienced Paediatric Patients 12 Years of Age and Older

In study GS-US-104-0321 (study 321), 87 treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm³ and the mean baseline plasma HIV-1 RNA was 4.6 log₁₀ copies/mL. The median DAVG₂₄ and DAVG₄₈ in plasma HIV-1 RNA were -1.58 and -1.42 log₁₀ copies/mL, respectively, for the tenofovir disoproxil fumarate treatment group compared with -1.55 and -1.35 log₁₀ copies/mL, respectively, for the placebo group at weeks 24 and 48. Overall, the trial failed to show a difference in virologic response between the two treatment groups. Subgroup analyses suggest the lack of difference in virological response may be attributable to imbalances between treatment arms in baseline viral susceptibility to tenofovir disoproxil fumarate and OBR. In patients with partially active or non-active OBR (genotypic sensitivity score ≤ 1), the addition of tenofovir disoproxil fumarate or placebo resulted in a median DAVG₂₄ in plasma HIV RNA of -1.66 and -1.14 log₁₀ copies/mL, respectively. Although changes in HIV-1 RNA in these highly treatment-experienced patients were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of tenofovir disoproxil fumarate in paediatric patients ≥ 12 years of age who weigh ≥ 35 kg whose HIV-1 isolate is expected to be sensitive to tenofovir disoproxil fumarate.

HIV-1 isolates from 43 patients who had plasma HIV-1 RNA ≥ 400 copies/mL were evaluated for tenofovir resistance-associated substitutions. One patient developed the K65R substitution by Week 48.

Treatment-Naïve Adult Patients

Study 903: Tenofovir DF + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicentre study comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus d4T, lamivudine and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4 cell count was 279 cells/mm³ (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads > 100,000 copies/mL and 39% had CD4 cell counts < 200 cells/mm³. Treatment outcomes through 144 weeks are presented in Table 6 below.

Table 6: Outcomes of Randomized Treatment (Study 903)

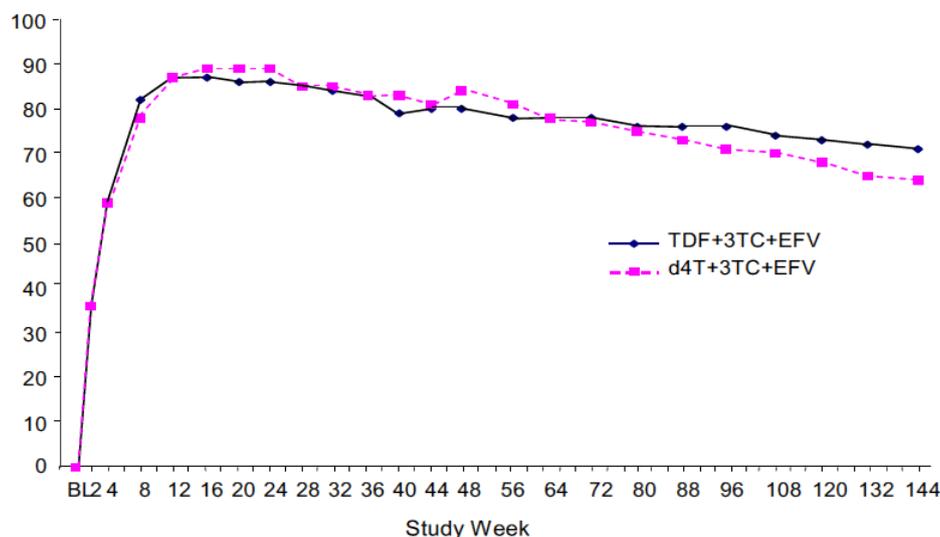
Outcomes	At Week 48		At Week 144	
	Tenofovir DF + Lamivudine + EFV (n = 299)	d4T + Lamivudine + EFV (n = 301)	Tenofovir DF + Lamivudine + EFV (n = 299)	d4T + Lamivudine + EFV (n = 301)
Responder ¹	79% ⁴	82% ⁴	68% ⁵	62% ⁵
Virologic failure ²	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	< 1%	1%	< 1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons ³	8%	7%	14%	15%

1. Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.
4. Difference -3.0% (-9.2% to 3.1%) p = 0.48. The difference and confidence interval are stratum weighted on baseline HIV-1 RNA and CD4.
5. Difference 6.1% (-1.4% to 13.7%) p = 0.11. The difference and confidence interval are stratum weighted on baseline HIV-1 RNA and CD4.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (\leq or $>$ 100,000 copies/mL) and CD4 cell count ($<$ or \geq 200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of patients in the tenofovir disoproxil fumarate and d4T arms, respectively, achieved and maintained confirmed HIV-1 RNA $<$ 50 copies/mL. The mean increase from baseline in CD4 cell count was 263 cells/mm³ for the tenofovir disoproxil fumarate arm and 283 cells/mm³ for the d4T arm.

The percentage of patients who achieved and maintained confirmed HIV RNA $<$ 400 using intent-to-treat analysis through 144 weeks of treatment in Study 903 is presented in Figure 2 below. Genotypic analyses of patients with virologic failure showed development of efavirenz-associated and lamivudine-associated mutations to occur most frequently and with no difference between the treatment arms. The K65R mutation occurred in 8 patients on the tenofovir disoproxil fumarate arm and in 2 patients on the d4T arm. Of the 8 patients who developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and the last one at Week 96. Among these patients, 5/8 patients subsequently gained full virologic control ($<$ 50 copies/mL) upon switching to new regimens that included a protease inhibitor in combination with nucleoside reverse transcriptase inhibitors through a median of 155 weeks of follow-up. One patient in the tenofovir disoproxil fumarate arm developed the K70E substitution in the virus. From both genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir disoproxil fumarate.

Figure 2: Percentage of Patients with HIV RNA $<$ 400 using Intent-to-treat Analysis through Week 144 (Study 903)
(Missing = Failure, Switch = Failure)



Study 934: Tenofovir DF + Emtricitabine + Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz

Study 934 is a randomized, open-label, active controlled multicentre study comparing two different dosing regimens in 511 antiretroviral-naïve HIV-1 infected patients. Patients were randomized to receive either emtricitabine + tenofovir disoproxil fumarate administered in combination with efavirenz or lamivudine/zidovudine administered in combination with efavirenz. For patients randomized to receive emtricitabine + tenofovir disoproxil fumarate the two drugs were administered individually for the first 96 weeks and then switched to tenofovir disoproxil fumarate/emtricitabine (fixed dose combination of tenofovir DF 300 mg/emtricitabine 200 mg) during Weeks 96 to 144, without regard to food.

For inclusion in the study, antiretroviral treatment-naïve adult patients (\geq 18 years) with plasma HIV RNA greater than 10,000 copies/mL, must have an estimated glomerular filtration rate as measured by Cockcroft-Gault method of \geq 50 mL/min, adequate haematologic function, hepatic transaminases and alanine aminotransferases \leq 3 ULN, total bilirubin \leq 1.5 mg/dL, serum amylase \leq 1.5 ULN and serum phosphorus \geq 2.2 mg/dL. Exclusion criteria included: a new AIDS defining condition diagnosed within 30 days (except on the basis of CD4 criteria), ongoing therapy with nephrotoxic drugs or agents that interacted with efavirenz, pregnancy/lactation, a history of clinically significant renal/bone disease or malignant disease other than Kaposi's sarcoma or basal-cell carcinoma, or a life expectancy of less than one year. If efavirenz associated central nervous system toxicities occurred, nevirapine could be

substituted for efavirenz. Patients who were not receiving their originally assigned treatment regimen after Week 48 or 96 and during the 30-day extension study window were not eligible to continue to weeks 96 or 144 respectively.

Patients had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm³ (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm³); 41% had CD4 cell counts < 200 cells/mm³ and 51% of patients had baseline viral loads > 100,000 copies/mL. Treatment outcomes at 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 7.

Table 7: Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934) in Treatment-Naïve Patients

Outcome at Weeks 48 and 144	At Week 48		At Week 144	
	Tenofovir DF + Emtricitabine + EFV (n = 244)	Lamivudine/ Zidovudine + EFV (n = 243)	Tenofovir DF/ Emtricitabine ⁴ + EFV (n = 227)	Lamivudine/ Zidovudine + EFV (n = 229)
Responder ¹	84%	73%	71%	58%
Virologic failure ²	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death ³	< 1%	1%	1%	1%

1. Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL.
2. Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL.
3. All deaths were unrelated to study drugs.
4. Patients received tenofovir DF + emtricitabine up to Week 96 and switched to tenofovir DF/emtricitabine from Week 96 to 144.

In this study, tenofovir disoproxil fumarate + emtricitabine in combination with efavirenz was statistically significantly superior to lamivudine/zidovudine in combination with efavirenz with regard to the primary and secondary endpoints: achieving and maintaining HIV-1 RNA < 400 copies/mL through 48 and 144 weeks (Table 7). The difference in the proportions of responders between the tenofovir disoproxil fumarate + emtricitabine group and the lamivudine/zidovudine group was 11.4%, and the 95% CI was 4.3–18.6% (p = 0.002) at Week 48 and a difference of 12.9% (95% CI was 4.2–21.6%, p = 0.004) at Week 144.

Through 48 weeks of therapy, 80% and 70% of patients in the tenofovir disoproxil fumarate + emtricitabine and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA < 50 copies/mL. The difference in the proportions of responders between the tenofovir DF + emtricitabine group and the lamivudine/zidovudine group was 9.1%, and the 95% CI was 1.6–16.6% (p = 0.021) at Week 48. The proportion of patients responding at 144 weeks of therapy was higher in the tenofovir DF/emtricitabine group (64%) compared with the lamivudine/zidovudine group (56%); p = 0.082, a difference of 8.1% and the 95% CI was -0.8–17.0%.

The mean increase from baseline in CD4 cell count was 190 cells/mm³ and 312 cells/mm³ for the tenofovir disoproxil fumarate + emtricitabine + efavirenz arm, and 158 cells/mm³ and 271 cells/mm³ for the lamivudine/zidovudine + efavirenz arm (p = 0.002 and p = 0.088) at Weeks 48 and 144 respectively.

Resistance analysis was performed on HIV isolates from all patients with > 400 copies/mL of HIV-1 RNA at Week 144 while on study drug or after treatment switch. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed in both treatment groups. Resistance to efavirenz occurred in 68% (13/19) analysed patients in the tenofovir DF/emtricitabine group and in 72% (21/29) analysed patients in the lamivudine/zidovudine group. The M184V mutation, associated with resistance to emtricitabine and lamivudine, developed significantly less in the analysed patients in the tenofovir DF/emtricitabine group 11% (2/19) compared with the analysed patients in the lamivudine/zidovudine group, 34% (10/29). Two patients in the lamivudine/zidovudine group developed thymidine analogue mutations, specifically D67N or K70R

mutations in the reverse transcriptase gene. No patient in either treatment group developed the K65R or K70E mutation, which is associated with reduced susceptibility to tenofovir disoproxil fumarate.

Genotypic Analyses of Tenofovir DF in Patients with Previous Antiretroviral Therapy (Studies 902 and 907)

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (n = 222) in treatment-experienced patients participating in Studies 902 and 907. In both of these studies, 94% of the participants evaluated had baseline HIV isolates expressing at least one NRTI mutation. These included resistance mutations associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), the lamivudine/abacavir-associated mutation (M184V) and others. In addition the majority of participants evaluated had mutations associated with either PI or NNRTI use. Virologic responses for patients in the genotype sub-study were similar to the overall results in Studies 902 and 907.

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Descriptions of numerical differences in HIV RNA response are displayed in Table 8. Because of the large number of potential comparisons, statistical testing was not conducted.

Varying degrees of cross-resistance to tenofovir disoproxil fumarate from pre-existing zidovudine-associated mutations were observed and appeared to depend on the number and type of mutations. Tenofovir DF-treated patients whose HIV expressed 3 or more zidovudine-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F or K219Q/E/N mutation did not appear to affect responses to tenofovir disoproxil fumarate therapy. The HIV RNA responses by number and type of baseline zidovudine-associated mutations are shown in Table 8.

Table 8: HIV RNA Response at Week 24 by Number of Baseline Zidovudine-Associated Mutations in Studies 902 and 907 (Intent-To-Treat)¹

Number of Baseline Zidovudine-associated Mutations ²	Change in HIV RNA ³ (n)	
	Tenofovir DF	Placebo
None	-0.80 (68)	-0.11 (29)
Any	-0.50 (154)	0 (81)
1 – 2	-0.66 (55)	-0.04 (33)
≥ 3 including M41L or L210W	-0.21 (57)	+0.01 (29)
≥ 3 without M41L or L210W	-0.67 (42)	+0.07 (19)

1. Genotypic testing performed by Virco Laboratories and Visible Genetics TruGene™ technology.
2. M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in RT.
3. Average HIV RNA change from baseline through Week 24 (DAVG₂₄) in log₁₀ copies/mL.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in patients with HIV that expressed the lamivudine/abacavir-associated M184V mutation. In the absence of zidovudine-associated mutations, patients with the M184V mutation receiving tenofovir disoproxil fumarate showed a -0.84 log₁₀ copies/mL decrease in their HIV RNA relative to placebo. In the presence of zidovudine-associated mutations, the M184V mutation did not affect the mean HIV RNA responses to tenofovir disoproxil fumarate treatment. HIV-1 RNA responses among these patients were durable through Week 48.

There were limited data on patients expressing some primary nucleoside reverse transcriptase inhibitor mutations and multi-drug resistant mutations at baseline. However, patients expressing mutations at K65R (n = 6), or L74V without zidovudine-associated mutations (n = 6) appeared to have reduced virologic responses to tenofovir disoproxil fumarate.

The presence of at least one HIV protease inhibitor or non-nucleoside reverse transcriptase inhibitor mutation at baseline did not appear to affect the virologic response to tenofovir disoproxil fumarate. Cross-resistance between tenofovir disoproxil fumarate and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Phenotypic Analyses of Tenofovir DF in Patients with Previous Antiretroviral Therapy (Studies 902 and 907)

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline phenotype (n = 100) in treatment-experienced patients participating in Studies 902 and 907. Phenotypic analysis of baseline HIV from patients in Studies 902 and 907 demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 9 summarizes the HIV RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 9: HIV RNA Response at Week 24 by Baseline Tenofovir DF Susceptibility in Studies 902 and 907 (Intent-To-Treat)¹

Baseline Tenofovir DF Susceptibility ²	Change in HIV RNA ³ (n)
≤ 1	-0.74 (35)
> 1 and ≤ 3	-0.56 (49)
> 3 and ≤ 4	-0.3 (7)
≤ 4	-0.61 (91)
> 4	-0.12 (9)

1. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram™ assay (Virco)
2. Fold change in susceptibility from wild-type
3. Average HIV RNA change from baseline through Week 24 (DAVG₂₄) in log₁₀ copies/mL

Clinical Efficacy in Chronic Hepatitis B

The demonstration of benefit of tenofovir disoproxil fumarate is based on histological, virological, biochemical and serological responses in adults with HBeAg positive and HBeAg negative chronic hepatitis B with compensated and decompensated liver function; clinical evidence of prior treatment failure; and patients co-infected with HIV-1 and HBV. In these clinical studies patients had active viral replication at baseline. Tenofovir disoproxil fumarate has demonstrated anti-HBV activity in patients with HBV containing lamivudine- or adefovir-resistance-associated mutations.

Study 0102 and 0103: Tenofovir DF Compared with Adefovir dipivoxil

Results through 48 weeks from two randomized, phase III double-blind studies comparing tenofovir disoproxil fumarate to adefovir dipivoxil (ADV) in patients with compensated liver disease are presented in Table 10 below. Study GS-US-174-0103 (0103) was conducted in 266 (randomized and treated) HBeAg positive patients while study GS-US-174-0102 (0102) was conducted in 375 (randomized and treated) patients negative for HBeAg and positive for HBeAb.

In both of these studies tenofovir disoproxil fumarate was statistically significantly superior to adefovir dipivoxil for the primary efficacy endpoint of complete response, (defined as HBV DNA levels < 400 copies/mL and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score). Treatment with tenofovir disoproxil fumarate 300 mg was also associated with significantly greater proportions of patients with HBV DNA < 400 copies/mL, when compared to adefovir dipivoxil 10 mg treatment. Both treatments produced similar results with regard to histological response (defined as Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score) at Week 48 (see Table 10 below).

In Study 0103 a significantly greater proportion of patients in the tenofovir disoproxil fumarate group than in the adefovir group had normalized ALT and achieved HBsAg loss at Week 48 (see Table 10 below).

Table 10: Clinical Outcomes of Randomized Treatment (Study 0102 and 0103) at Week 48

Parameter	Study 0102 (HBeAg Negative)		Study 0103 (HBeAg Positive)	
	Tenofovir DF n = 250	Adefovir n = 125	Tenofovir DF n = 176	Adefovir n = 90
Complete Response (%) ¹	71*	49	67*	12
Histology Histological Response (%) ²	72	69	74	68
HBV DNA (%) < 400 copies/mL (< 69 IU/mL)	93*	63	76*	13
ALT (%) Normalized ALT ³	76	77	68*	54
Serology (%) HBeAg Loss/Seroconversion	N/A	N/A	22/21	18/18
HBsAg Loss/Seroconversion	0/0	0/0	3*/1	0/0

* p value vs adefovir dipivoxil < 0.05.

- 1 Complete response defined as HBV DNA levels < 400 copies/mL and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
- 2 Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
- 3 The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.

Tenofovir disoproxil fumarate was associated with statistically significantly greater proportions of patients with undetectable HBV DNA (< 169 copies/mL [< 29 IU/mL]; the limit of quantification of the Roche COBAS TaqMan HBV assay), when compared with adefovir dipivoxil (Study 0102; 91% and 56%, respectively and Study 0103; 69% and 9%, respectively).

Response to treatment with tenofovir disoproxil fumarate was comparable in nucleoside-experienced (n = 51) and nucleoside-naïve (n = 375) patients and in patients with normal ALT (n = 21) and abnormal ALT (n = 405) at baseline when Studies 0102 and 0103 were combined. Forty-nine of the 51 nucleoside-experienced patients were previously treated with lamivudine. Seventy-three percent of nucleoside-experienced and 69% of nucleoside-naïve patients achieved complete response to treatment; 90% of nucleoside-experienced and 88% of nucleoside-naïve patients achieved HBV DNA suppression < 400 copies/mL. All patients with normal ALT at baseline and 88% of patients with abnormal ALT at baseline achieved HBV DNA suppression < 400 copies/mL.

Treatment Beyond 48 weeks (Studies 0102 and 0103)

In Studies 0102 (n = 347) and 0103 (n = 238), after receiving double-blind treatment for 48 weeks (either tenofovir disoproxil fumarate or adefovir dipivoxil), patients rolled over with no treatment interruption, to open-label tenofovir disoproxil fumarate.

In Study 0102, 266 of 347 patients (77%) continued through Week 384, while in Study 0103, 146 of 238 (61%) continued through Week 384. At Weeks 96, 144, 192, 240, 288 and 384 viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil fumarate treatment (see Tables 11 and 12 below).

Table 11: Virological, Biochemical and Serological Response at Weeks 96, 144, 192, 240, 288 and 384 (Study 0102)

Outcomes ^a	Study 0102 (HBeAg Negative)											
	Tenofovir DF (n = 250)						Adefovir Rollover to Tenofovir DF (n = 125)					
Week	96 ^b	144 ^e	192 ^h	240 ^j	288 ^k	384 ⁿ	96 ^c	144 ^f	192 ^h	240 ^j	288 ^l	384 ^o
HBV DNA (%) < 400 copies/mL (< 69 IU/mL)	90	87	84	83	80	74	89	88	87	84	84	76
HBV DNA (%) < 169 copies/mL (< 29 IU/mL)	89	86	83	82	80	74	89	88	87	84	84	76
ALT (%) Normalized ALT ^d	72	73	67	70	68	64	68	70	77	76	74	69
Serology (%)^p HBsAg Loss	0	0	0	0	0	1	0	0	0	0	1	1
Seroconversion ^q	0	0	0	0	0	0	0	0	0	0 ^m	1	1

- a Based upon Long-Term Evaluation Algorithm (LTE Analysis) – Patients who discontinued the study at any time prior to Week 288 due to a protocol defined endpoint, as well as those completing Week 288, are included in the denominator.
- b 48 weeks double-blind tenofovir DF followed by up to 48 weeks open-label.
- c 48 weeks double-blind adefovir followed by up to 48 weeks open-label tenofovir DF.
- d The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.
- e 48 weeks double-blind tenofovir DF followed by 96 weeks open-label.
- f 48 weeks double-blind adefovir followed by 96 weeks open-label tenofovir DF.
- g 48 weeks double-blind tenofovir DF followed by 144 weeks open-label.
- h 48 weeks double-blind adefovir followed by 144 weeks open-label tenofovir DF.
- i 48 weeks double-blind tenofovir DF followed by 192 weeks open-label.
- j 48 weeks double-blind adefovir followed by 192 weeks open-label tenofovir DF.
- k 48 weeks double-blind tenofovir DF followed by 240 weeks open-label [n = 192/235 (82%)].
- l 48 weeks double-blind adefovir followed by 240 weeks open-label tenofovir DF [n = 101/112 (91%)].
- m One patient in this group became HBsAg negative for the first time at the 240-week visit and was ongoing in the study at the time of the data cut-off. However, the subject's HBsAg loss was ultimately confirmed at the subsequent visit.
- n 48 weeks double-blind tenofovir DF followed by 336 weeks open-label tenofovir DF.
- o 48 weeks double-blind adefovir followed by 336 weeks open-label tenofovir DF.
- p Figures presented are cumulative percentages based upon a Kaplan-Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir DF (KM-TDF).
- q Figures presented are cumulative percentages based upon a Kaplan-Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir DF (KM-TDF).
- n/a = Not Applicable

Patients with HBV DNA \geq 400 copies/mL at Week 72 or later were eligible to receive intensification therapy with open-label tenofovir DF/emtricitabine and results from these patients are not included as responders in this table (intensification therapy = failure). Results from the tenofovir DF 384-week treatment groups including these patients were 81% for HBV DNA < 400 copies/mL and 70% for normalized ALT, for Study 0102.

Table 12: Virological, Biochemical and Serological Response at Weeks 96, 144, 192, 240, 288 and 384 (Study 0103)

Outcomes ^a	Study 0103 (HBeAg Positive)											
	Tenofovir DF (n = 176)						Adefovir Rollover to Tenofovir DF (n = 90)					
Week	96 ^b	144 ^e	192 ^h	240 ^j	288 ^l	384 ^o	96 ^c	144 ^f	192 ⁱ	240 ^k	288 ^m	384 ^p
HBV DNA (%) < 400 copies/mL (< 69 IU/mL)	76	72	68	64	61	56	74	71	72	66	65	61
HBV DNA (%) < 169 copies/mL (< 29 IU/mL)	73	70	68	63	61	56	74	70	70	66	65	61
ALT (%) Normalized ALT ^d	60	55	56	46	47	47	65	61	59	56	57	56
Serology (%) HBeAg Loss	26	29	34	38	37	30	24	33	36	38	40	35
Seroconversion	23	23	25	30	25	20	20	26	30	31	31	24
HBsAg Loss	5	8 ^g	11 ^g	11 ⁿ	12 ⁿ	15 ⁿ	6	8 ^g	8 ^g	10 ⁿ	11 ⁿ	13 ⁿ
Seroconversion	4	6 ^g	8 ^g	8 ⁿ	8 ⁿ	12 ⁿ	5	7 ^g	7 ^g	10 ⁿ	10 ⁿ	11 ⁿ

- a Based upon Long-Term Evaluation Algorithm (LTE Analysis) – Patients who discontinued the study at any time prior to Week 288 due to a protocol defined endpoint, as well as those completing Week 288, are included in the denominator.
- b 48 weeks double-blind tenofovir DF followed by up to 48 weeks open-label.
- c 48 weeks double-blind adefovir followed by up to 48 weeks open-label tenofovir DF.
- d The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.
- e 48 weeks double-blind tenofovir DF followed by 96 weeks open-label.
- f 48 weeks double-blind adefovir followed by 96 weeks open-label tenofovir DF.
- g Figures presented are cumulative percentages based upon a Kaplan Meier analysis (KM-ITT).
- h 48 weeks double-blind tenofovir DF followed by 144 weeks open-label.
- i 48 weeks double-blind adefovir followed by 144 weeks open-label tenofovir DF.
- j 48 weeks double-blind tenofovir DF followed by 192 weeks open-label.
- k 48 weeks double-blind adefovir followed by 192 weeks open-label tenofovir DF.
- l 48 weeks double-blind tenofovir DF followed by 240 weeks open-label [n = 106/154 (69)].
- m 48 weeks double-blind adefovir followed by 240 weeks open-label tenofovir DF [n = 67/84 (80)].
- n Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir DF (KM-TDF).
- o 48 weeks double-blind tenofovir DF followed by 336 weeks open-label tenofovir DF.
- p 48 weeks double-blind adefovir followed by 336 weeks open-label tenofovir DF.
- n/a = Not Applicable

Patients with HBV DNA \geq 400 copies/mL at Week 72 or later were eligible to receive intensification therapy with open-label tenofovir DF/emtricitabine and results from these patients are not included as responders in this table (intensification therapy = failure). Results from the tenofovir DF 384-week treatment groups including these patients were 69% for HBV DNA < 400 copies/mL and 52% for normalized ALT and 38%/27% for HBeAg loss/seroconversion.

Paired baseline and Week 240 liver biopsy data were available for 331/489 patients who remained in Studies 0102 and 0103 (see Table 13 below). Ninety-five percent (225/237) of patients without cirrhosis at baseline and 99% (93/94) of patients with cirrhosis at baseline had either no change or an improvement in fibrosis (Ishak fibrosis score). Of the 94 patients with cirrhosis at baseline (Ishak fibrosis score 5–6), 26% (24) experienced no change in Ishak fibrosis score and 72% (68) experienced reversal of cirrhosis by Week 240 with a reduction in Ishak fibrosis score of at least 2 points except for one patient with an initial Ishak score of five.

Table 13: Histological Response (%) in Compensated HBeAg negative and HBeAg positive Subjects at Week 240 Compared to Baseline

	Study 0102 (HBeAg negative)		Study 0103 (HBeAg positive)	
	Tenofovir DF n = 250 ^c	Adefovir Rollover to Tenofovir DF n = 125 ^d	Tenofovir DF n = 176 ^c	Adefovir Rollover to Tenofovir DF n = 90 ^d
Histological response ^{a,b}	88% [130/148]	85% [63/74]	90% [63/70]	92% [36/39]

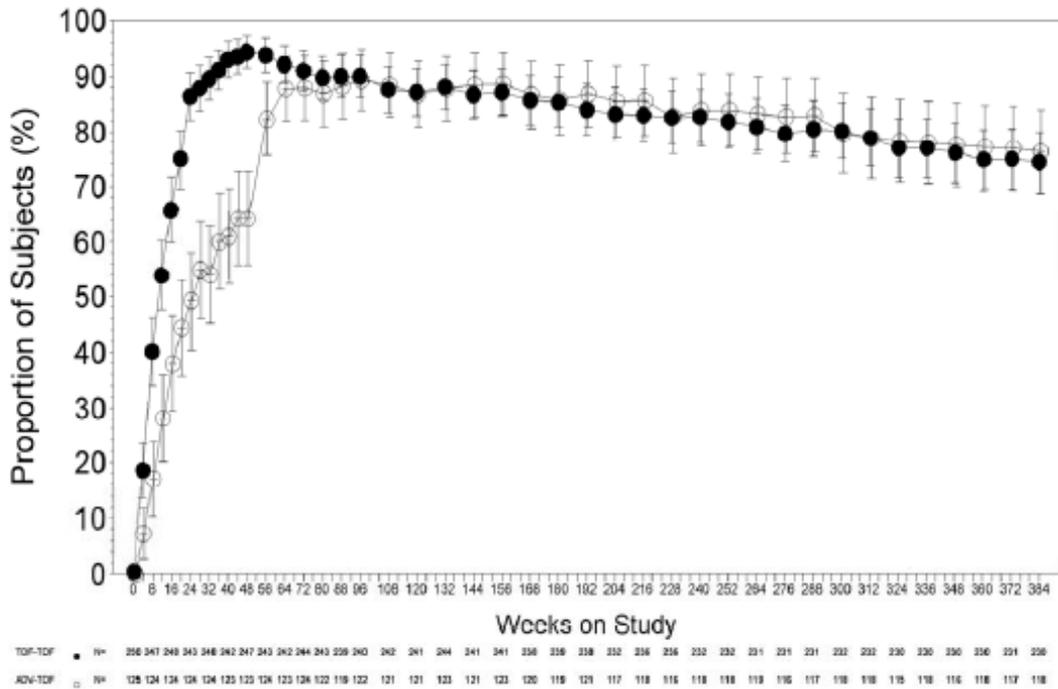
- a The population used for analysis of histology included only patients with available liver biopsy data (Missing = Excluded) by Week 240. Response after addition of emtricitabine is excluded (total of 17 subjects across both studies).
- b Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
- c 48 weeks double-blind tenofovir DF followed by up to 192 weeks open-label.
- d 48 weeks double-blind adefovir followed by up to 192 weeks open-label tenofovir DF.

When the data were evaluated including only patients that completed 384 weeks of therapy (observed (missing data is excluded) and data after the addition of emtricitabine included; on therapy analysis), in the group of patients who received 48 weeks of double-blind treatment with tenofovir disoproxil fumarate followed by open-label treatment with tenofovir disoproxil fumarate; 99% (173/174) and 100% (88/88) of patients had HBV DNA < 400 copies/mL and 88% (141/160) and 81% (70/86) of patients had ALT normalization at Week 384, in Studies 0102 and 0103 respectively. In Study 0103, HBeAg loss was reported for 44% (31/70) of patients and 28% (19/68) of patients experienced HBeAg seroconversion. 14% of patients experienced HBsAg loss and 12% of patients experienced HBsAg seroconversion by Week 384. In study 102, HBsAg loss and seroconversion were 1% in both treatment groups.

Similarly (using the on-therapy analysis), in the group of patients who received 48 weeks of double-blind treatment with adefovir dipivoxil followed by open-label treatment with tenofovir disoproxil fumarate; 100% (90/90) and 95% (55/58) of patients had HBV DNA < 400 copies/mL and 88% (74/84) and 88% (50/57) of patients had ALT normalization, at Week 384, in Studies 0102 and 0103 respectively. In Study 0103, HBeAg loss was reported for 50% (24/48) of patients and 36% (17/47) of patients experienced seroconversion. HBsAg loss was experienced in 13% and 11% of patients experienced HBsAg seroconversion, while on tenofovir disoproxil fumarate.

The proportion of patients in Studies 0102 and 0103 with HBV DNA < 400 copies/mL are shown in Figures 3 and 4.

Figure 3: Proportion of Patients (95% CI) with HBV DNA < 400 copies/mL by Visit Full Analysis Set (Study 0102)

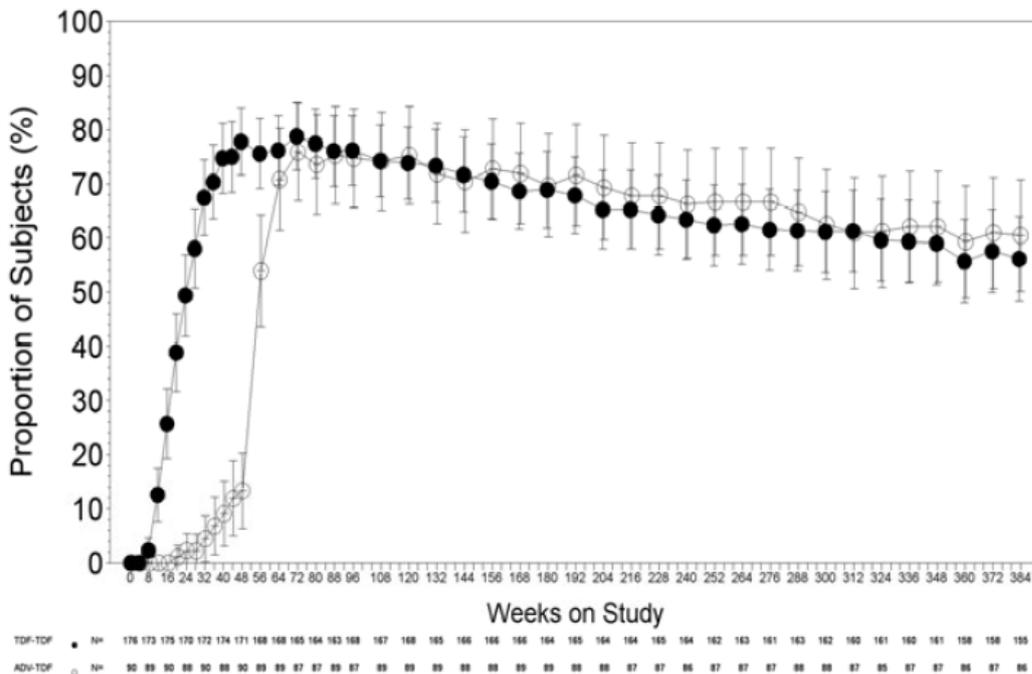


Randomized and treated patients, LTE Algorithm (Long-Term Evaluation/Addition of FTC=Failure (LTE-TDF); 384-week data is also reported in Table 11.

TDF*: 48 weeks double-blind tenofovir DF followed by up to 336 weeks open-label

ADV*: 48 weeks double-blind adefovir dipivoxil followed by up to 336 weeks open-label tenofovir DF.

Figure 4: Proportion of Patients (95% CI) with HBV DNA < 400 copies/mL by Visit Full Analysis Set (Study 0103)



Randomized and treated patients, LTE Algorithm (Long-Term Evaluation/Addition of FTC=Failure (LTE-TDF); 384-week data is also reported in Table 12.

TDF*: 48 weeks double-blind tenofovir DF followed by up to 336 weeks open-label

ADV*: 48 weeks double-blind adefovir dipivoxil followed by up to 336 weeks open-label tenofovir DF.

Nucleos(t)ide Experienced Patients

Experience with Patients with Lamivudine Resistance (Study GS-US-174-0121)

The efficacy and safety of tenofovir disoproxil fumarate or 200 mg emtricitabine plus 300 mg tenofovir disoproxil fumarate were evaluated in a randomized, double-blind study, in HBeAg-positive and HBeAg-negative patients with viremia (HBV DNA \geq 1,000 IU/mL) and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). One hundred and forty-one adult subjects were randomized to the tenofovir disoproxil fumarate treatment arm. The mean age of subjects randomized to tenofovir disoproxil fumarate was 47 years (range 18-73), 74% were male, 59% were Caucasian, and 37% were Asian. At baseline, 54% of subjects were HBeAg-negative, 46% were HBeAg-positive, and 56% had abnormal ALT. Subjects had a mean HBV DNA of 6.4 log₁₀ copies/mL and mean serum ALT of 71 U/L at baseline.

After 96 weeks of treatment, 126 of 141 subjects (89%) randomized to tenofovir disoproxil fumarate had HBV DNA < 400 copies/mL, and 49 of 79 subjects (62%) had ALT normalization. Among the HBeAg-positive subjects randomized to tenofovir disoproxil fumarate, 10 of 65 subjects (15%) experienced HBeAg loss, and 7 of 65 subjects (11%) experienced anti-HBe seroconversion through Week 96.

Experience with Patients Co-infected with HIV and HBV (Study ACTG 5127)

In a randomized, 48-week double-blind, non-inferiority trial, tenofovir disoproxil fumarate 300 mg daily was compared with adefovir dipivoxil 10 mg daily in the treatment of chronic hepatitis B patients who were co-infected with HIV and were stable on antiretroviral therapy. Mean baseline serum HBV DNA were 9.45 log₁₀ copies/mL and 8.85 log₁₀ copies/mL in subjects randomized to tenofovir disoproxil fumarate (n = 27) and ADV (n = 25), respectively. In subjects for whom there was Week 48 data (n = 35), the mean change from baseline in serum HBV DNA was -5.74 log₁₀ copies/mL for the tenofovir disoproxil fumarate group (n = 18) and -4.03 log₁₀ copies/mL for the adefovir dipivoxil group (n = 17), respectively. A total of 61 % of subjects (36% in the tenofovir disoproxil fumarate group and 25% in the adefovir dipivoxil group) had normalized serum ALT at Week 48, but the differences were not statistically significant. The study showed that over 48 weeks, treatment with either adefovir dipivoxil or tenofovir disoproxil fumarate resulted in clinically important suppression of serum HBV DNA and tenofovir disoproxil fumarate was not inferior to adefovir dipivoxil in HBV viral suppression.

Experience in Patients who had Incomplete Viral Response to Adefovir dipivoxil (Study 0106)

The efficacy and safety of tenofovir disoproxil fumarate 300 mg or tenofovir DF/emtricitabine is being evaluated in a randomized, double-blind study (Study GS-US-174-0106, 0106), in HBeAg positive and HBeAg negative patients who had persistent viraemia (HBV DNA \geq 1000 copies/mL) while receiving adefovir dipivoxil 10 mg for more than 24 weeks. Overall at Week 48, treatment with tenofovir disoproxil fumarate resulted in 66% (35/53) of patients with HBV DNA < 400 copies/mL and 64% (34/53) of patients with undetectable HBV DNA (below 169 copies/mL the limit of quantification of the Roche COBAS TaqMan HBV assay); patients that discontinued prior to 48 weeks, including those who received intensification therapy tenofovir DF/emtricitabine were excluded. In addition, at Week 48, the percentage of patients who had ALT normalization was 33% (9/27).

In Study 0106, patients were also analysed based upon lamivudine- or adefovir-resistant HBV results at baseline; patients that discontinued prior to 48 weeks were considered as failures. Table 14 below summarizes Week 48 results of patients treated with tenofovir disoproxil fumarate.

At Week 48, no patient with lamivudine- or adefovir-resistant mutations at baseline, had HBeAg/HBsAg loss and/or seroconversion.

Table 14: Summary of Clinical Efficacy at Week 48 (Study 0106): RAT Analysis Set

	Tenofovir DF (n = 53)
HBV DNA <400 copies/mL, n(%)¹	43 (81%)
Lamivudine-resistant patients, n/N (%) ¹	6/7 (86%)
Adefovir-resistant patients, n/N (%) ¹	7/8 (88%)
HBV DNA <169 copies/mL, n(%)¹	40 (76%)
Lamivudine-resistant patients, n/N (%) ¹	5/7 (72%)
Adefovir-resistant patients, n/N (%) ¹	7/8 (88%)
Normalized ALT^{1,2}	11/27 (41%)
Lamivudine-resistant patients, n/N (%) ¹	3/4 (75%)
Adefovir-resistant patients, n/N (%) ¹	3/5 (60%)
HBeAg Loss^{1,3}	3/38 (8%)
HBeAg Seroconversion^{1,3}	2/38 (5%)
HBeAg Loss^{1,3}	1/53 (2%)
HBsAg Seroconversion^{1,3}	1/53 (2%)

- 1 Patients who prematurely discontinued the study prior to Week 48 were considered failures at all time points following the time of discontinuation.
- 2 Normalized ALT defined as ALT at or below the ULN, for subjects with above the ULN at baseline.
- 3 HBeAg/HBsAg loss defined as HBeAg/HBsAg result for those subjects with positive HBeAg/HBsAg at baseline.
Seroconversion defined as HBeAg/HBsAg loss and positive anti-HBe/anti-HBs result.

Experience in Patients with Decompensated Liver Disease at 48 weeks (Study 0108)

Study GS-US-174-0108 (0108) is a randomized, double-blind, active controlled study evaluating the safety and efficacy of tenofovir disoproxil fumarate (n = 45) for 48 weeks in patients with decompensated liver disease. In the tenofovir disoproxil fumarate treatment arm, patients had a mean Child-Pugh-Turcotte (CPT) score of 7.2, mean HBV DNA of 5.8 log₁₀ copies/mL and mean serum ALT of 61 U/L at baseline. Forty-two percent (19/45) of patients had at least 6 months of prior lamivudine experience and 9 of 45 patients (20%) had lamivudine and/or adefovir resistance substitutions at baseline. The co-primary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/dL.

In the tenofovir disoproxil fumarate treatment arm, 3 of 45 patients (7%) discontinued treatment due to an adverse event; 4 of 45 (9%) experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/mL through Week 48; these results were similar to those in the non-tenofovir disoproxil fumarate containing treatment arm. HBV DNA < 400 copies/mL and normal ALT were observed in 31 of 44 patients (70%) and 25 of 44 patients (57%), respectively, in the tenofovir disoproxil fumarate treatment arm. The mean change from baseline in CPT score was -0.8; the mean absolute CPT score was 6 at Week 48.

After 168 weeks, 16% (7/45) of the tenofovir disoproxil fumarate group, 4% (2/45) of the emtricitabine plus tenofovir disoproxil fumarate group, and 14% (3/22) of the entecavir group experienced tolerability failure. Thirteen percent (6/45) of the tenofovir disoproxil fumarate group, 13% (6/45) of the emtricitabine plus tenofovir disoproxil fumarate group and 9% (2/22) of the entecavir group had a confirmed increase in serum creatinine ≥ 0.5 mg/dL or confirmed serum phosphate of < 2 mg/dL.

Experience in Paediatric Patients 12 Years of Age and Older (Study 0115)

In Study GS-US-174-0115 (0115), 106 HBeAg negative and positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 10⁵ copies/mL, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil fumarate (n = 52) or placebo (n = 54) for 72 weeks. At Week 72, 88% (46/52) of patients in the tenofovir disoproxil fumarate treatment group and 0% (0/54) of patients in the placebo group had HBV DNA < 400 copies/mL. Seventy-four percent (26/35) of patients in the tenofovir disoproxil fumarate group had normalized ALT at Week 72 compared to 31% (13/42) in the placebo group. Response to treatment with tenofovir disoproxil fumarate was comparable in nucleos(t)ide-naïve patients (n = 20) and nucleos(t)ide-experienced (n = 32) patients. Ninety-five percent of nucleos(t)ide-naïve patients and 84%

nucleos(t)ide-experienced patients achieved HBV DNA < 400 copies/mL at Week 72. At Week 72, 96% (27/28) of immune-active patients (HBV DNA $\geq 10^5$ copies/mL, serum ALT > 1.5x ULN) in the tenofovir disoproxil fumarate treatment group and 0% (0/32) of patients in the placebo group had HBV DNA < 400 copies/mL. Seventy-five percent (21/28) of immune-active patients in the tenofovir disoproxil fumarate group had normal ALT at Week 72 compared to 34% (11/32) in the placebo group.

Clinical Resistance

Of 279 HBeAg negative and HBeAg positive patients who received treatment with tenofovir disoproxil fumarate for up to 384 weeks in Studies 0102 and 0103, genotypic analysis was performed on HBV isolates for all patients with HBV DNA > 400 copies/mL (n = 2). No amino acid substitutions occurred in these subjects' isolates which were associated with tenofovir resistance.

In Studies 0102 and 0103, 152 patients treated with adefovir dipivoxil for 48 weeks, rolled over to treatment with tenofovir disoproxil fumarate for up to 366 weeks; two patients with HBV DNA remaining > 400 copies/mL was evaluated for resistance. No amino acid substitutions occurred in these subjects' isolates which were associated with tenofovir resistance.

Among the 53 treatment-experienced patients in Study 0106 treated with tenofovir disoproxil fumarate, 17 had HBV DNA > 400 copies/mL following up to 48 weeks of treatment with tenofovir disoproxil fumarate. Among these patients, no amino acid substitutions were observed in association with tenofovir resistance.

In Study 0108, 45 patients (including 9 patients with lamivudine and/or adefovir resistance substitutions at baseline) received tenofovir disoproxil fumarate for up to 168 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 8 of 9 patients with HBV DNA > 400 copies/mL. No amino acid substitutions associated with tenofovir resistance were identified in these isolates.

In Studies 0102, 0103 and 0106, 12 patients randomized to tenofovir disoproxil fumarate had HBV containing lamivudine-resistance associated substitutions at baseline. Following up to 48 weeks (0106; n = 7) or 240 weeks (0102 and 0103; n = 4) of treatment with tenofovir disoproxil fumarate, two patients in Study 0106 had HBV DNA > 400 copies/mL; no amino acid substitutions were observed in association with tenofovir resistance.

In Studies 0102, 0103 and 0106, 13 patients treated with tenofovir disoproxil fumarate had adefovir-resistance associated substitutions at baseline. Following up to 48 weeks (0106; n = 8) or 240 weeks (0102 and 0103; n = 5) of treatment with tenofovir disoproxil fumarate, one patient in Study 0103 and two patients in Study 0106 had HBV DNA > 400 copies/mL; no amino acid substitutions were observed in association with tenofovir resistance.

In a paediatric study (GS-US-174-0115), HBV isolates from 5 patients who had plasma HBV DNA > 400 copies/mL were evaluated for tenofovir resistance-associated substitutions. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates by Week 72.

In Study 0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil fumarate for up to 96 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/9 patients with HBV DNA > 400 copies/mL at their last time point on tenofovir disoproxil fumarate. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

Cross Resistance

Cross-resistance has been observed among HBV reverse transcriptase inhibitors. In cell based assays, HBV strains expressing the rtV173L, rtL180M and rtM204I/V mutations associated with resistance to lamivudine, telbivudine and reduced susceptibility to entecavir showed a susceptibility to tenofovir ranging from 0.7 to 3.4-fold that of wild type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6 to 6.9-fold that of wild type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9 to 10-fold that of wild type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC₅₀ values 1.5-fold that of wild type virus.

INDICATIONS

Tenofovir disoproxil fumarate in combination with other antiretroviral agents is indicated for the treatment of HIV-infected adults and paediatric patients 12 years of age and older.

Tenofovir disoproxil fumarate is indicated for the treatment of chronic hepatitis B in adults (see **CLINICAL TRIALS**).

Tenofovir disoproxil fumarate is indicated for the treatment of chronic hepatitis B in paediatric patients 12 years of age and older with compensated liver disease and with evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels or evidence of active inflammation.

CONTRAINDICATIONS

Known hypersensitivity to tenofovir, tenofovir disoproxil fumarate or to any of the excipients in the film-coated tablets.

Tenofovir disoproxil fumarate must not be administered to children less than 12 years of age until further data become available.

This medicine should not be administered concurrently with fixed dose combination tablets containing tenofovir disoproxil fumarate or adefovir dipivoxil.

PRECAUTIONS

General

Patients receiving tenofovir disoproxil fumarate or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should be advised that antiretroviral therapies, including tenofovir disoproxil fumarate, have not been proven to prevent the risk of transmission of HIV or HBV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that tenofovir disoproxil fumarate is not a cure for HIV infection.

HIV antibody testing should be offered to all HBV-infected patients before initiating tenofovir disoproxil fumarate therapy (see **HIV and HBV Co-infection**, below).

In the treatment of chronic hepatitis B, limited data are currently available in immuno-suppressed patients or those receiving immuno-suppressive regimens, orthotrophic liver transplant patients and patients co-infected with the hepatitis C or D virus. As clinical studies have not included sufficient numbers of subjects to determine whether these patients respond differently to tenofovir disoproxil fumarate chronic hepatitis B therapy, such patients should be closely monitored.

Impaired Renal Function

Dosing interval adjustment is required in all patients with creatinine clearance < 50 mL/min (see **DOSAGE AND ADMINISTRATION**). The proposed dose interval modifications are based on limited data and may not be optimal. The safety and efficacy of these dosing interval adjustment guidelines have not been clinically evaluated, and so the potential benefit of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of tenofovir disoproxil fumarate (see **ADVERSE EFFECTS: Post Marketing Experience**).

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during tenofovir disoproxil fumarate therapy. Patients at risk for, or with a history

of, renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, should be routinely monitored for changes in serum creatinine and phosphorus.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including tenofovir disoproxil fumarate, in the treatment of HIV infection. A majority of these cases have been reported in women. The preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues is low for tenofovir disoproxil fumarate. However, as tenofovir is structurally related to nucleoside analogues, this risk cannot be excluded. Caution should be exercised when administering tenofovir disoproxil fumarate to any patient, and particularly to those with known risk factors for liver disease. Treatment with tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

HIV and HBV Co-infection

Due to the risk of development of HIV resistance, tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients.

Exacerbation of Hepatitis After Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including tenofovir disoproxil fumarate may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Early Virologic Failure

Clinical studies in HIV infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-NRTI or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance mutations have been reported in clinical studies of combinations of tenofovir, lamivudine and abacavir or tenofovir, lamivudine and didanosine. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Immune Reconstitution Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Lipodystrophy

In HIV-infected patients redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Bone Effects

Bone toxicities including a reduction in bone mineral density (BMD) have been observed in studies in three animal species (see **Animal Toxicology**, below). Clinically relevant bone abnormalities have not been seen in long term clinical studies in adults (> 3 years).

Bone abnormalities may be associated with proximal renal tubulopathy (see **ADVERSE EFFECTS: Post-Marketing Surveillance**). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

There is limited clinical experience with tenofovir disoproxil fumarate in paediatric patients. In a clinical study of HIV-1 infected paediatric patients 12 years of age and older (Study 0321), bone effects were similar to adult patients. Under normal circumstances BMD increases rapidly in this age group. In this study, the mean rate of bone gain was less in the tenofovir disoproxil fumarate treated group compared to the placebo group. Six tenofovir disoproxil fumarate treated patients and one placebo treated patient had significant (> 4%) lumbar spine BMD loss in 48 weeks. Markers of bone turnover in tenofovir disoproxil fumarate treated paediatric patients 12 years of age and older suggest increased bone turnover, consistent with the bone effects observed in adults. The effects of tenofovir disoproxil fumarate associated changes in BMD and biochemical markers on long-term bone health and fracture risk are unknown. In a clinical study (Study 115) conducted in paediatric subjects 12 years of age and older with chronic HBV infection, both the tenofovir disoproxil fumarate and placebo treatment arms experienced an overall increase in mean spine BMD, as expected for an adolescent population. The percent increase from baseline in spine BMD in tenofovir disoproxil fumarate treated subjects was less than the increase observed in placebo-treated subjects. During the study, three subjects in the tenofovir disoproxil fumarate group and two subjects in the placebo group had a decrease of more than 4% in lumbar spine BMD.

Effects on Fertility

Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir disoproxil fumarate dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

Use in Pregnancy (Category B3)

No clinical data are available for pregnant women being treated with tenofovir disoproxil fumarate. Reproductive toxicity studies performed in rats and rabbits did not reveal any evidence of harm to the foetus due to tenofovir at respective exposures (AUC) of 4–13 and 66-fold the human exposure. Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced foetal serum phosphorus concentrations. Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed.

Use in Lactation

In animal studies tenofovir was excreted in milk after oral administration of tenofovir disoproxil fumarate (rats) and after subcutaneous administration of tenofovir base (non-human primates). In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low concentrations (estimated neonatal concentrations 128–266x lower than the tenofovir IC₅₀ (50% maximal inhibitory concentration)). Tenofovir associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown. It is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

Paediatric Use

The safety and efficacy of tenofovir disoproxil fumarate in paediatric patients aged 12 to < 18 years is supported by data from two randomized studies in which tenofovir disoproxil fumarate was administered to HIV infected treatment-experienced patients and patients with chronic hepatitis B (see **CLINICAL TRIALS** and **ADVERSE EFFECTS**). The safety and efficacy of tenofovir disoproxil fumarate has not been established in children less than 12 years of age.

The clinical relevance of the long term effects of tenofovir disoproxil fumarate treatment on BMD are unknown and, at present, the data on the reversibility of renal toxicity effects is limited. Therefore, a multidisciplinary approach is recommended to consider the benefit/risk balance of treatment.

As hepatitis B is a chronic disease of the liver, ongoing clinical monitoring is recommended

Use in the Elderly

Tenofovir disoproxil fumarate has not been studied in patients over the age of 65. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased

hepatic, renal or cardiac function and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION**).

Genotoxicity

Tenofovir disoproxil fumarate was mutagenic in an *in vitro* mouse L5178Y lymphoma cell assay (*tk* locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage. Tenofovir base was not active in *in vitro* bacterial assays for gene mutation, and an equivocal response was seen in the *in vitro* mouse L5178Y lymphoma assay at a high concentration.

Carcinogenicity

In a long-term carcinogenicity study conducted in mice with tenofovir disoproxil fumarate there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15× the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5× the human systemic exposure at the therapeutic dose based on AUC).

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) between 6- and 12-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Effects on Ability to Drive and Use Machines

No studies on the effects on ability to drive or use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate.

INTERACTIONS WITH OTHER MEDICINES

Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir is excreted renally. Co-administration of tenofovir disoproxil fumarate with medicinal products that decrease or compete for renal clearance may increase serum concentrations of tenofovir. Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with abacavir, didanosine, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives, ribavirin, and tacrolimus (refer to Tables 2 and 3).

When administered with tenofovir disoproxil fumarate, C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation at a dose of 400 mg daily increased significantly (see Table 4). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily. In patients weighing ≥ 60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with tenofovir disoproxil fumarate. Data are not available to recommend a dose adjustment of didanosine for adult or paediatric patients weighing < 60 kg. When co-administered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (< 400 kcal, 20% fat). Co-administration of didanosine buffered tablet formulation with tenofovir disoproxil fumarate should be under fasted conditions. **Co-administration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving**

this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.

Tenofovir disoproxil fumarate affects the pharmacokinetics of atazanavir. Tenofovir disoproxil fumarate should only be administered with boosted atazanavir (ATZ 300 mg/RTV 100 mg). The safety and efficacy of this regimen has been substantiated over 48 weeks in a clinical study.

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs.

ADVERSE EFFECTS

From Clinical Studies

Clinical Trials in Adult Patients with HIV Infection

More than 12,000 patients have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase I–III clinical trials and expanded access studies. A total of 1,544 patients have received tenofovir disoproxil fumarate 300 mg once daily in Phase I–III clinical trials; over 11,000 patients have received tenofovir disoproxil fumarate in expanded access studies.

Treatment-Experienced Adult Patients

Treatment-Emergent Adverse Events: The most common adverse events that occurred in patients receiving tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in Table 15 (below).

Table 15: Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in \geq 3% in Any Treatment Group in Study 907 (0–48 weeks)

	Tenofovir DF (n = 368) (Week 0–24)	Placebo (n = 182) (Week 0–24)	Tenofovir DF (n = 368) (Week 0–48)	Placebo Crossover to Tenofovir DF (n = 170) (Week 24–48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal Pain	4%	3%	7%	6%
Back Pain	3%	3%	4%	2%
Chest Pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhoea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%

	Tenofovir DF (n = 368) (Week 0–24)	Placebo (n = 182) (Week 0–24)	Tenofovir DF (n = 368) (Week 0–48)	Placebo Crossover to Tenofovir DF (n = 170) (Week 24–48)
Insomnia	3%	2%	4%	4%
Peripheral Neuropathy ¹	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash Event ²	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight Loss	2%	1%	4%	2%

1. Peripheral neuropathy includes peripheral neuritis and neuropathy.
2. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesicubullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 16 below.

Table 16: Grade 3 / 4 Laboratory Abnormalities Reported in ≥ 1% of Tenofovir DF-Treated Patients in Study 907 (0-48 weeks)

	Tenofovir DF (n = 368) (Week 0–24)	Placebo (n = 182) (Week 0–24)	Tenofovir DF (n = 368) (Week 0–48)	Placebo Crossover to Tenofovir DF (n = 170) (Week 24–48)
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (> 750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	7%	14%	12%	12%
Serum Amylase (> 175 U/L)	6%	7%	7%	6%
Urine Glucose (≥ 3+)	3%	3%	3%	2%
AST (M: > 180 U/L) (F: > 170 U/L)	3%	3%	4%	5%
ALT (M: > 215 U/L) (F: > 170 U/L)	2%	2%	4%	5%
Serum Glucose (> 250 U/L)	2%	4%	3%	3%
Neutrophils (< 750 mg/dL)	1%	1%	2%	1%

Treatment-Naïve Adult Patients

Treatment-Emergent Adverse Events: In a double-blind active controlled study in which 600 treatment-naïve patients received tenofovir disoproxil fumarate (n = 299) or d4T (n = 301) in combination with lamivudine and efavirenz for 144 weeks (Study 903), the adverse reactions seen were generally consistent, with the addition of dizziness, with those seen in treatment-experienced patients (Table 17).

Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhoea and nausea.

Table 17: Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in ≥ 5% in Any Treatment Group in Study 903 (0-144 weeks)

	Tenofovir DF + Lamivudine + EFV (n = 299)	d4T + Lamivudine + EFV (n = 301)
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Back Pain	9%	8%
Fever	8%	7%
Abdominal Pain	7%	12%
Asthenia	6%	7%
Digestive System		
Diarrhoea	11%	13%
Nausea	8%	9%
Vomiting	5%	9%
Dyspepsia	4%	5%
Metabolic Disorders		
Lipodystrophy	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Anxiety	6%	6%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy ¹	1%	5%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash Event ²	18%	12%

1. Peripheral neuropathy includes peripheral neuritis and neuropathy

2. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash

Laboratory Abnormalities: With the exception of triglyceride elevations that were more common in the d4T group (14%) compared with tenofovir disoproxil fumarate (3%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and d4T treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 18.

Table 18: Grade 3 / 4 Laboratory Abnormalities Reported in ≥1% of Tenofovir DF-Treated Patients in Study 903 (0–144 weeks)

	Tenofovir DF + Lamivudine + EFV (n = 299)	d4T + Lamivudine + EFV (n = 301)
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	12%	12%
Serum Amylase (> 175 U/L)	9%	8%
AST (M: > 180 U/L) (F: > 170 U/L)	5%	7%
ALT (M: > 215 U/L) (F: > 170 U/L)	4%	5%
Haematuria (> 100 RBC/HPF)	7%	7%
Neutrophils (< 750 mg/dL)	3%	1%
Triglycerides (> 750 mg/dL)	3%	13%

Study 934 - Treatment Emergent Adverse Events: Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either tenofovir disoproxil fumarate + emtricitabine administered in combination with efavirenz (n = 257) or lamivudine/zidovudine administered in combination with efavirenz (n = 254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table 19). Adverse events leading to study drug discontinuation occurred in significantly smaller number of patients in the tenofovir DF/emtricitabine group compared to the lamivudine/zidovudine group (5% vs 11%, p = 0.010). The most frequently occurring adverse event leading to study drug discontinuation was anaemia (including decreased haemoglobin), no patient in the tenofovir DF/emtricitabine group and 6% of patients in the lamivudine/zidovudine group.

Table 19: Frequency of Adverse Reactions to Emtricitabine and/or Tenofovir DF (Grade 2–4) Occurring in ≥ 3% of Patients Receiving Emtricitabine and Tenofovir DF (or Tenofovir DF/Emtricitabine) in Study 934 (0-144 Weeks)¹

Adverse Reaction	Tenofovir DF/ Emtricitabine ² + EFV (n = 257)	Lamivudine/Zidovudine + EFV (n = 254)
Gastrointestinal Disorders		
Diarrhoea	9%	5%
Nausea	9%	7%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Insomnia	5%	7%
Abnormal Dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

1. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
2. Patients received tenofovir DF + emtricitabine up to Week 96 and switched to tenofovir DF/emtricitabine from Week 96 to 144.

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 20).

Table 20: Grade 3/4 Laboratory Abnormalities Reported in > 1% of Patients in Either Treatment Group, Study 934 (0–144 Weeks)

	Tenofovir DF/ Emtricitabine ¹ + EFV (n = 254)	Lamivudine/Zidovudine + EFV (n = 251)
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	9%	7%
Serum Amylase (> 175 U/L)	8%	4%
AST (M: > 180 U/L) (F: > 170 U/L)	3%	3%
ALT (M: > 215 U/L) (F: > 170 U/L)	2%	3%
Hyperglycaemia (> 250 mg/dL)	2%	1%
Haematuria (> 75 RBC/HPF)	3%	2%
Neutrophils (< 750 mm ³)	3%	5%
Triglycerides (> 750 mg/dL)	5%	3%
Haemoglobin (< 7.0 g/dL)	0%	2%

1. Patients received tenofovir DF + emtricitabine up to Week 96 and switched to Tenofovir DF/emtricitabine from Week 96 to 144.

Clinical Trials in Paediatric Patients 12 Years of Age and Older with HIV Infection

Assessment of adverse reactions is based on one randomized study (Study 321) in 87 HIV-infected paediatric patients (12 to 18 years of age) who received treatment with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in paediatric patients 12 years of age and older who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies in adults. Bone effects similar to those seen in adults were observed in this study (see **PRECAUTIONS**).

Clinical Trials in Adult Patients with Hepatitis B

Assessment of adverse reactions is based on experience in two double-blind comparative controlled Studies (0102 and 0103) in which 641 patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir disoproxil fumarate 300 mg daily (n = 426) or adefovir dipivoxil 10 mg daily (n = 215) for 48 weeks (see Table 21).

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and frequency. Frequencies are defined as common (≥ 1/100, < 1/10).

Gastrointestinal disorders:

Common: nausea.

Table 21: Most frequent (> 5%) Treatment-Emergent Adverse Events of Any Severity (Integrated RAT analysis set; 48-week Data from Studies 0102 and 0103)

AEs by Preferred Term ^a (n, %) ^b	Overall Tenofovir DF (n = 426)	Overall ADV (n = 215)
Any Adverse Event	317 (74.4%)	158 (73.5%)
Headache	55 (12.9%)	30 (14.0%)
Nasopharyngitis	42 (9.9%)	24 (11.2%)
Nausea	40 (9.4%)	6 (2.8%)
Fatigue	36 (8.5%)	16 (7.4%)
Abdominal Pain Upper	30 (7.0%)	11 (5.1%)
Back Pain	30 (7.0%)	10 (4.7%)
Diarrhoea	28 (6.6%)	11 (5.1%)
Dizziness	24 (5.6%)	7 (3.3%)
Procedural Pain	16 (3.8%)	12 (5.6%)
Pharyngolaryngeal Pain	15 (3.5%)	11 (5.1%)
Upper Respiratory Tract Infection	13 (3.1%)	11 (5.1%)

a Events coded using MedDRA dictionary version 9.1.

b Subjects are counted once only for each system organ class and preferred term, counting the most severe occurrence.

Laboratory Abnormalities: A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 22.

Table 22: Grade 3/4 Laboratory Abnormalities Reported in > 1% of Tenofovir DF-Treated Patients in Studies 0102 and 0103 (0–48 weeks)

	Tenofovir DF (n = 426)	ADV (n = 215)
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	2%	3%
Serum Kinase (> 175 U/L)	4%	1%
Glycosuria (≥ 3+)	3%	<1%
AST (M: > 180 U/L) (F: > 170 U/L)	4%	4%
ALT (M: > 215 U/L) (F: > 170 U/L)	10%	6%

Treatment beyond 48 weeks: The adverse reactions observed with continued treatment for 384 weeks were consistent with the safety profile of tenofovir disoproxil fumarate. Grade 3/4 laboratory abnormalities were similar in nature and frequency in patients continuing treatment for up to 288 weeks in these studies.

Nucleos(t)ide-Experienced Patients: No new adverse reactions to tenofovir disoproxil fumarate were identified in those patients in Studies 0102, 0103 and 0106 and 0121 who had been previously treated with adefovir dipivoxil, lamivudine or other nucleoside analogues (n = 493).

Patients with Decompensated Liver Disease: No new adverse reactions to tenofovir disoproxil fumarate were identified from a double-blind active-controlled study (0108) in which patients with decompensated liver disease received treatment with tenofovir disoproxil fumarate (n = 45) for 48 weeks. Among the 45 subjects receiving tenofovir disoproxil fumarate, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus

(16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the study due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus < 2mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score \geq 10 and MELD score \geq 14 at entry) developed renal failure. Because both tenofovir disoproxil fumarate and decompensated liver disease may have an impact on renal function, the contribution of tenofovir disoproxil fumarate to renal impairment in this population is difficult to ascertain.

One of 45 subjects experienced an on-treatment hepatic flare during the 48 Week study.

At week 168, in this population of patients with decompensated liver disease, the rate of death was of 13% (6/45) in the tenofovir disoproxil fumarate group, 11% (5/45) in the emtricitabine plus tenofovir disoproxil fumarate group and 14% (3/22) in the entecavir group. The rate of serious hepatocellular carcinoma was 18% (8/45) in the tenofovir disoproxil fumarate group, 7% (3/45) in the emtricitabine plus tenofovir disoproxil fumarate group and 9% (2/22) in the entecavir group. The rate of serious ascites, which was experienced in 7% (3/45) in the tenofovir disoproxil fumarate group, 7% (3/45) in the emtricitabine plus tenofovir disoproxil fumarate group and 5% (1/22) in the entecavir group. The rate of serious hepatic encephalopathy was 7% (3/45) in the tenofovir disoproxil fumarate group, 2% (1/45) in the emtricitabine plus tenofovir disoproxil fumarate group and 9% (2/22) in the entecavir group (see **CLINICAL TRIALS**).

Clinical Trials in Paediatric Patients 12 Years of Age and Older with HBV Infection

Assessment of adverse reactions is based on one randomized study (Study 0115) in 106 paediatric patients (12 to < 18 years of age) infected with chronic hepatitis B receiving treatment with tenofovir disoproxil fumarate (n = 52) or placebo (n = 54) for 72 weeks. The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies in adults (see **ADVERSE REACTIONS**).

Post-Marketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of tenofovir disoproxil fumarate. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Immune System Disorders

Allergic reaction (including angioedema)

Metabolism and Nutrition Disorders

Hypokalaemia, hypophosphataemia, lactic acidosis

Respiratory, Thoracic and Mediastinal Disorders

Dyspnoea

Gastrointestinal Disorders

Increased amylase, abdominal pain, pancreatitis,

Hepatobiliary Disorders

Hepatic steatosis, increased liver enzymes (most commonly AST, ALT, gamma GT), hepatitis

Skin and Subcutaneous Tissue Disorders

Rash

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures)

Renal and Urinary Disorders

Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

General Disorders and Administration Site Conditions

Asthenia

Reactions as a consequence of Proximal Renal Tubulopathy: The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.

Immune Reconstitution Syndrome: In HIV infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to infectious pathogens (active or inactive) may arise (see **PRECAUTIONS**).

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see **PRECAUTIONS**).

Adverse reactions attendant to class

Nephrotoxicity (elevation in serum creatinine and urine protein, and decrease in serum phosphorus) is the dose-limiting toxicity associated with other nucleotide analogues [cidofovir and high doses of adefovir dipivoxil evaluated for HIV disease (60 mg and 120 mg)].

DOSAGE AND ADMINISTRATION

Adults

The recommended dose is 300 mg (one tablet) once daily taken orally. In order to optimize the absorption of tenofovir, it is recommended that the tablet be taken with food.

Paediatric Patients (≥ 12 Years of Age and ≥ 35 kg)

The recommended dose for paediatric patients (12 years of age and older), who weigh ≥ 35 kg, is 300 mg (one tablet) once daily taken orally. In order to optimize the absorption of tenofovir, it is recommended that the tablet be taken with food.

The safety and efficacy of tenofovir disoproxil fumarate in patients under the age of 12 years have not been established. Tenofovir disoproxil fumarate must not be administered to children under 12, until further data become available.

Elderly

No data are available on which to make a dose recommendation for patients over the age of 65 years. The safety and efficacy of tenofovir disoproxil fumarate have not been established in patients over the age of 65 years. Caution should be exercised when administering tenofovir disoproxil fumarate to elderly patients until further data become available describing the disposition of tenofovir disoproxil fumarate in these patients (see **PRECAUTIONS**). The greater frequency of decreased hepatic, renal or cardiac function in these patients, presence of any concomitant illnesses or the need for treatment with other medicinal products concomitantly with tenofovir disoproxil fumarate should be taken into consideration.

Renal impairment

Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. Dosing interval adjustment is required in all patients with creatinine clearance < 50 mL/min (calculated using the Cockcroft Gault equation), as detailed in Table 23 below. The proposed dose interval modifications are based on limited data and may not be optimal. The safety and efficacy of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients (see **PRECAUTIONS**).

Table 23: Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) ¹			Haemodialysis Patients
	≥ 50	30–49	10–29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72–96 hours	Every 7 days or after a total of approximately 12 hours of dialysis ²

1. Calculated with Cockcroft Gault equation.
2. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. Tenofovir DF should be administered following completion of dialysis

The pharmacokinetics of tenofovir have not been evaluated in non-haemodialysis patients with creatinine clearance < 10 mL/min; therefore, no dosing recommendation is available for these patients.

No data are available to make dose recommendations in paediatric patients 12 years of age and older with renal impairment.

Hepatic Impairment

There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

Chronic Hepatitis B

Treatment with tenofovir disoproxil fumarate may be discontinued if there is HBsAg loss or HBsAg seroconversion, otherwise the optimal duration of treatment is unknown.

OVERDOSAGE

Symptoms

Clinical experience of doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available from two studies. In one study, intravenous tenofovir, equivalent to 16.7 mg/kg/day tenofovir disoproxil fumarate, was administered daily for 7 days. In the second study, 600 mg tenofovir disoproxil fumarate was administered to patients orally for 28 days.

No unexpected or severe adverse reactions were reported in either study. The effects of higher doses are not known.

Treatment

If overdose occurs the patient must be monitored for evidence of toxicity (see **ADVERSE EFFECTS** and **PRECAUTIONS**), and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Tenofovir APOTEX tablets are intended for oral administration.

Each tablet contains 300 mg tenofovir disoproxil fumarate as the active ingredient.

Light blue, almond shaped, biconvex, coated tablet. Engraved “TEN” over “300” on one side, “APO” on the other side.

Bottle (white, round HDPE bottle with white or blue PP child-resistant cap and desiccant) of 30 tablets. AUST R 247315.

Blister Pack (aluminium/aluminium silver foil) of 30 tablets. AUST R 247314.

Not all pack types may be available.

Storage

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

29 April 2016

DATE OF MOST RECENT AMENDMENT:

10 January 2018