

DATA SHEET

VIREAD[®] (tenofovir disoproxil fumarate) 300 mg Tablets

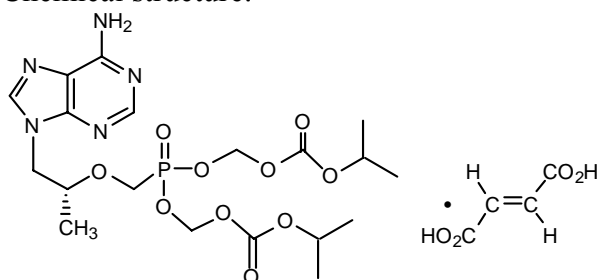
NAME OF THE MEDICINE

VIREAD 300 mg tablets

The active substance in VIREAD is tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a salt of a prodrug of tenofovir. Tenofovir disoproxil fumarate is designated chemically as 9-[(R)-2-[[bis[[isopropoxycarbonyl]oxy]methoxy]-phosphinyl]-methoxy]propyl]adenine fumarate (1:1).

Chemical structure:



Molecular formula: C₂₃H₃₄O₁₄N₅P

Molecular mass: 635.52

CAS 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*.

VIREAD tablets contain the following ingredients as excipients: *Core*: microcrystalline cellulose (E460), pregelatinised maize starch, croscarmellose sodium, lactose and magnesium stearate (E572). *Coating*: Opadry II Y-30-10671-A-(ARTG3968).

Each VIREAD tablet is light blue and almond-shaped. Each tablet is debossed on one side with the markings “GILEAD” and “4331” and on the other side with the marking “300”. The tablets are supplied in bottles with screw cap closures.

PHARMACOLOGY

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 of VIREAD, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from VIREAD in fasted patients was approximately 25%. Following oral administration of a single dose of VIREAD 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.

Effects of Food on Oral Absorption: Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40 to 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 VIREAD 300 mg once daily in the fed state, when meal content was not controlled.

Distribution: After oral administration of VIREAD, 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 to 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 VIREAD 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 VIREAD 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 VIREAD dose over the dose range 75 to 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_{tau} are $0.38 \pm 0.13 \mu\text{g/mL}$ and $3.39 \pm 1.22 \mu\text{g}\cdot\text{hr/mL}$, respectively. Tenofovir exposure achieved in paediatric patients aged 12 years of age and older receiving oral daily doses of VIREAD 300 mg were similar to exposures achieved in adults receiving once-daily doses of VIREAD 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 VIREAD 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 \pm SD) of Tenofovir* 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
$AUC_{0-\infty}$ (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

*300 mg, single dose of VIREAD

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, 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 VIREAD 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 VIREAD dosing is required in patients with hepatic impairment.

Pharmacokinetic/pharmacodynamic relationship: VIREAD 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 PHARMACOKINETICS).

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of VIREAD 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.

VIREAD has been evaluated in healthy volunteers in combination with abacavir, didanosine, efavirenz, emtricitabine (Emtriva[®]), entecavir, indinavir, lamivudine (3TC), lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir and tacrolimus. Tables 2 and 3 summarise pharmacokinetic effects of co-administered drug on tenofovir pharmacokinetics and effects of VIREAD 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 summarises the drug interaction between VIREAD and didanosine. When administered with multiple doses of VIREAD, 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 VIREAD, 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 x 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 x 7 days	14	↔	↔	↔
Efavirenz	600 once daily x 14 days	29	↔	↔	↔
Emtricitabine (Emtriva)	200 once daily x 7 days	17	↔	↔	↔
Entecavir	1 mg once daily x 10 days	28	↔	↔	↔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↔	↔	↔
Lopinavir/Ritonavir	400/100 twice daily x 14 days	24	↔	↑ 32 (↑ 26 to ↑ 38)	↑ 51 (↑ 32 to ↑ 66)
Methadone ⁵	40-110 once daily x 14 days ⁶	13	↔	↔	↔
Nelfinavir	1250 twice daily x 14 days	29	↔	↔	↔
Oral Contraceptives ⁷	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen [®]) Once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NC
Saquinavir/Ritonavir	1000/100 twice daily x 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus ⁸	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔

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

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 VIREAD. 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 VIREAD

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 x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir ²	Atazanavir/Ritonavir ³ 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5) ³	↓ 25 (↓ 42 to ↓ 3) ³	↓ 23 (↓ 46 to ↑ 10) ³
Efavirenz	600 once daily x 14 days	30	↔	↔	↔
Emtricitabine (Emtriva)	200 once daily x 7 days	17	↔	↔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	↔	↑ 13 (↓ 11 to ↑ 15)	↔
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	↔ ↔	↔ ↔	↔ ↔
Methadone ⁴	40-110 once daily x 14 days ⁵	13	↔	↔	↔
Nelfinavir M8 Metabolite	1250 twice daily x 14 days	29	↔ ↔	↔ ↔	↔ ↔
Oral Contraceptives ⁶	Ethinyl Estradiol/ Norgestimate (Ortho- Tricyclen [®]) Once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Saquinavir	Saquinavir/Ritonavir 1000/100 twice daily x 14	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29 ⁷ (↑ 12 to ↑ 48)	↑ 47 ⁷ (↑ 23 to ↑ 76)

Ritonavir	days		↔	↔	↑ 23 (↑ 3 to ↑ 46)
Tacrolimus ⁸	0.05 mg/kg twice daily x 7 days	21	↔	↔	↔

- Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable
- REYATAZ™ Prescribing Information (Bristol-Myers Squibb)
- 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)
- R-(active), S-and total methadone exposures were equivalent when dosed alone or with VIREAD.
- 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 VIREAD.
- 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 coadministered.
- Subjects received tenofovir DF 300 mg once daily as the combination product TRUVADA.

Table 4. Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

Didanosine ¹ Dose (mg)/ Method of Administration ²	VIREAD Method of Administration ²	N	% Difference (90% CI) vs. Didanosine 400 mg alone, Fasted ³	
			C _{max}	AUC
Buffered tablets				
400 once daily ⁴ x 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 hr 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 hr 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)

- See PRECAUTIONS regarding use of didanosine with VIREAD.
- Administration with food was with a light meal (~373 kcal, 20% fat).
- Increase = ↑; Decrease = ↓; No Difference = ↔
- 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.

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 μM , 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 IC_{50} (50% inhibitory concentration) for tenofovir was in the range of 0.04 μM to 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 IC_{50} 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 analog-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 IC_{50} was observed. In 10 samples which had multiple thymidine-associated mutations (mean 3.4), a mean 3.7-fold increase of the IC_{50} was observed (range 0.8 to 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 (IC_{50} >10-fold compared with wild type). Tenofovir shows activity against non-nucleoside 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 can also be selected by zalcitabine, didanosine, and

abacavir, and causes reduced susceptibility to zalcitabine, didanosine, stavudine (d4T), abacavir, and lamivudine (14-, 4-, 2-, 3-, and 25-fold, respectively).

Anti-Hepatitis B Virus Activity In Vitro: The *in vitro* antiviral activity of tenofovir against laboratory strains of HBV was assessed in the HepG2 2.2.15 cell line. The EC₅₀ values for tenofovir were in the range 0.14 to 1.5 µM, with CC₅₀ (50% cytotoxicity concentration) values > 100 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 slightly synergistic effects were observed with the combination of tenofovir and emtricitabine.

CLINICAL TRIALS

Clinical efficacy in HIV Infection:

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

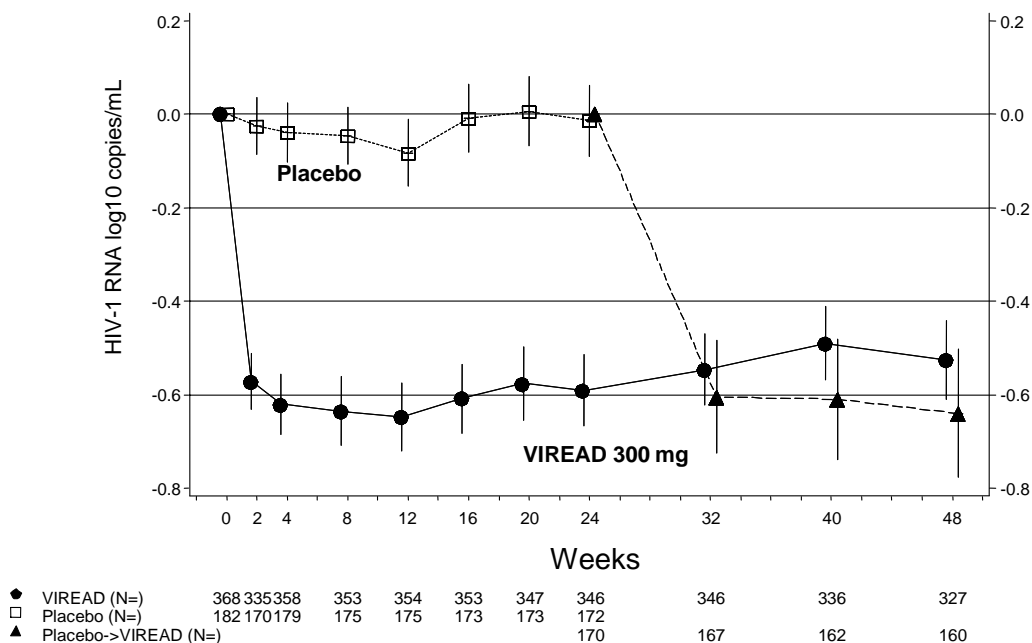
Treatment-Experienced Adult Patients

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

Study 907 was a 24 week, double-blind placebo-controlled multicentre study of VIREAD 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 VIREAD 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 (log₁₀ copies/mL) Through Week 48:
Study 907 (All Available Data)[†]



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

[†] Patients on placebo after 24 weeks received VIREAD. ITT population missing data = excluded.

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

Table 5. Outcomes of Randomized Treatment (Study 907)

Outcomes	0-24 weeks		0-48 weeks	24-48 weeks
	VIREAD (N=368) % (95% CI)	Placebo (N=182) % (95% CI)	VIREAD (N=368) %	Placebo Crossover to VIREAD (N=170) %
HIV-1 RNA <400 copies/mL ¹	40% ⁴ (35% to 45%)	11% ⁴ (6% to 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 Weeks 24 and 48 respectively.
2. Patients with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV-1 RNA at Weeks 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 VIREAD 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 VIREAD group and -5 cells/mm³ for the placebo group. Mean change in absolute CD4 counts by week 48 was +4 cells/mm³ for the VIREAD 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 VIREAD (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 for the VIREAD treatment group compared to -1.55 and -1.35 log₁₀ copies/mL for the placebo group at weeks 24 and 48, respectively. 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 VIREAD and OBR. In patients with partially active or non-active OBR (genotypic sensitivity score ≤ 1), the addition of VIREAD 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 VIREAD in paediatric patients ≥ 12 years of age who weigh ≥ 35 kg whose HIV-1 isolate is expected to be sensitive to VIREAD.

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: VIREAD + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicentre study comparing VIREAD (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	
	VIREAD+ 3TC+EFV (N=299)	d4T +3TC+EFV (N=301)	VIREAD+ 3TC+EFV (N=299)	d4T +3TC+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%

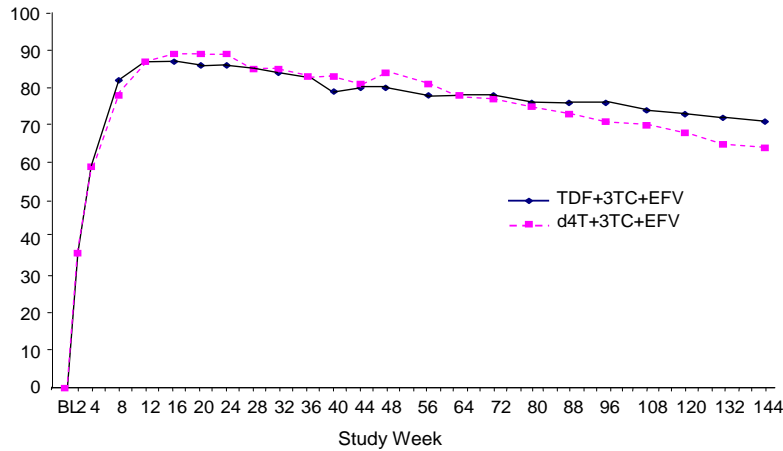
1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other 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 ≥ 200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of patients in the VIREAD 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 VIREAD 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 VIREAD arm and in 2 patients on the d4T arm. Of the 8 patients who developed K65R in the VIREAD 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. From both genotypic and phenotypic analyses there was no evidence for other pathways of resistance to VIREAD.

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: VIREAD + EMTRIVA + Efavirenz Compared with Combivir® (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 randomised to receive either EMTRIVA + VIREAD administered in combination with efavirenz or Combivir (lamivudine/zidovudine) administered in combination with efavirenz. For patients randomised to receive EMTRIVA + VIREAD the two drugs were administered individually for the first 96 weeks and then switched to TRUVADA (fixed dose combination of tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg) during weeks 96 to 144, without regard to food.

For inclusion in the study, antiretroviral treatment naïve adult patients (≥ 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 ≥ 50 mL/min, adequate haematologic function, hepatic transaminases and alanine aminotransferases ≤ 3 ULN, total bilirubin ≤ 1.5 mg/dL, serum amylase ≤ 1.5 ULN and serum phosphorus ≥ 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 to 80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm³ (range 2 to 1191) and

median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56 to 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 Randomised Treatment at Weeks 48 and 144 (Study 934) in Treatment Naïve Patients

Outcome at Weeks 48 and 144	WEEK 48		WEEK 144	
	VIREAD + EMTRIVA + EFV (N=244)	Combivir + EFV (N=243)	TRUVADA ⁴ + EFV (N=227)	Combivir + 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 VIREAD + EMTRIVA up to week 96 and switched to TRUVADA from week 96 to 144.

In this study, VIREAD + EMTRIVA in combination with efavirenz was statistically significantly superior to Combivir in combination with efavirenz with regards 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 VIREAD + EMTRIVA group and the Combivir group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at week 48 and a difference of 12.9% (95% CI was 4.2% to 21.6%, p=0.004) at week 144 .

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

The mean increase from baseline in CD4 cell count was 190 cells/mm³ and 312 cells/mm³ for the VIREAD + EMTRIVA + efavirenz arm, and 158 cells/mm³ and 271 cells/mm³ for the Combivir + 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 TRUVADA group and in 72% (21/29) analysed patients in the Combivir group. The M184V mutation, associated with resistance to emtricitabine and lamivudine, developed significantly less in the analysed patients in the TRUVADA group 11% (2/19) compared with the analysed patients in the Combivir group, 34% (10/29). Two patients in the Combivir group developed thymidine analog mutations, specifically D67N or K70R mutations in the reverse transcriptase gene. No patient in either treatment group developed the K65R mutation, which is associated with reduced susceptibility to VIREAD.

Genotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy (Study 902 and 907)

The virologic response to VIREAD therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment experienced patients participating in trials 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 substudy 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 VIREAD from pre-existing zidovudine-associated mutations were observed and appeared to depend on the number and type of mutations. VIREAD-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 VIREAD 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 VIREAD 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)	
	VIREAD	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 VIREAD 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 VIREAD 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 VIREAD 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 VIREAD.

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 VIREAD. Cross-resistance between VIREAD and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Phenotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy (Study 902 and 907)

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

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

Baseline VIREAD 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 VIREAD 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. VIREAD has demonstrated anti-HBV activity in patients with HBV containing lamivudine-or adefovir-resistance-associated mutations.

Study 0102 and 0103: VIREAD Compared with HEPSERA (adefovir dipivoxil)

Results through 48 weeks from two randomised, phase 3 double-blind studies comparing VIREAD to HEPSERA in patients with compensated liver disease are presented in Table 10 below. Study GS-US-174-0103 (0103) was conducted in 266 (randomised and treated) HBeAg positive patients while study GS-US-174-0102 (0102) was conducted in 375 (randomised and treated) patients negative for HBeAg and positive for HBeAb.

In both of these studies VIREAD was statistically significantly superior to HEPSERA 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 VIREAD 300 mg was also associated with significantly greater proportions of patients with HBV DNA < 400 copies/mL, when compared to HEPSERA 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 VIREAD group than in the HEPSERA group had normalized ALT and achieved HBsAg loss at Week 48 (see Table 10 below).

Table 10. Clinical Outcomes of Randomised Treatment (Study 0102 and 0103) at Week 48

Parameter	Study 0102 (HBeAg Negative)		Study 0103 (HBeAg Positive)	
	VIREAD N= 250	HEPSERA N= 125	VIREAD N= 176	HEPSERA 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 HEPSERA < 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.

³The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.

VIREAD 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 to HEPSERA (study 0102; 91%, 56% and study 0103; 69%, 9%) respectively.

Response to treatment with VIREAD 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 and 0103, after receiving double-blind treatment for 48 weeks (either VIREAD or HEPSERA), patients rolled over with no treatment interruption, to open-label VIREAD.

In study 0103, 82 % of patients randomised to VIREAD (and treated) completed 96 weeks of treatment. In study 0102, 315 of 375 patients (84%) continued treatment through week 192, while in study 0103, 198 of 266 (74%) continued treatment through week 192. At weeks 96, 144 and 192, viral suppression, biochemical and serological responses were maintained with continued VIREAD treatment (see Table 11 below).

Table 11. Virological, Biochemical and Serological Response at Week 96, 144 and 192 (Study 0102 and 0103)

Outcomes ^a	Study 0102 (HBeAg Negative)						Study 0103(HBeAg Positive)					
	VIREAD (N= 250)			HEPSERA Rollover to VIREAD (N= 125)			VIREAD (N= 176)			HEPSERA Rollover to VIREAD (N= 90)		
	96 wks ^b	144 wks ^e	192 wks ⁱ	96 wks ^c	144 wks ^e	192 wks ^h	96 wks ^b	144 wks ^e	192 wks ⁱ	96 wks ^c	144 wks ^f	192 wks ^h
HBV DNA (%) < 400 copies/mL (<69 IU/mL)	90	87	84	89	88	87	76	72	68	74	71	72
HBV DNA (%) < 169 copies/ml (<29 IU/mL)	89	86	83	89	88	87	73	70	68	74	70	70
ALT (%) Normalised ALT ^d	72	73	67	68	70	77	60	55	56	65	61	59
Serology (%) HBeAg Loss/ Seroconversion	N/A	N/A	N/A	N/A	N/A	N/A	26/23	29/23	34/25	24/20	33/26	36/30
HBsAg Loss/ Seroconversion	0/0	0/0	0/0	0/0	0/0	0/0	5/4	8/6 ^g	11/8 ^g	6/5	8/7 ^g	8/7 ^g

^a. Based upon Long-Term Evaluation Algorithm (LTE Analysis) – Patients who discontinued the study at any time prior to week 192 due to a protocol defined endpoint, as well as those completing week 192, are included in the denominator.

^b. 48 weeks double-blind VIREAD followed by up to 48 weeks open-label.

^c. 48 weeks double-blind HEPSEARA followed by up to 48 weeks open-label VIREAD.

^d. The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.

^e. 48 weeks double-blind VIREAD followed by 96 weeks open-label,

^f. 48 weeks double-blind HEPSEARA followed by 96 weeks open-label VIREAD,

^g. Figures presented are cumulative percentages based upon a Kaplan Meier analysis (KM-ITT),

^h. 48 weeks double-blind VIREAD followed by 144 weeks open-label,

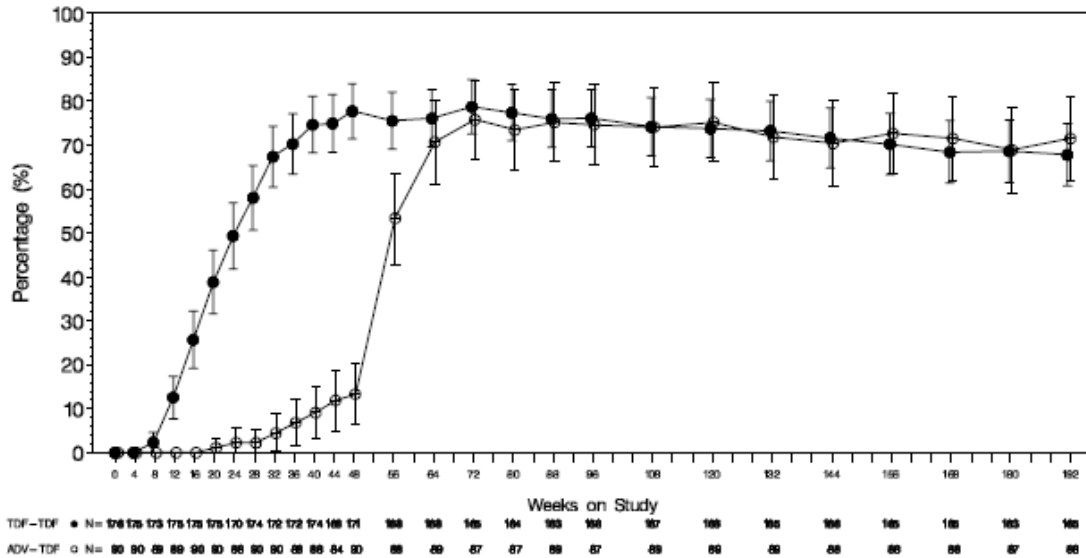
ⁱ. 48 weeks double-blind HEPSEARA followed by 144 weeks open-label VIREAD, N/A = Not Applicable

Patients with HBV DNA ≥400 copies/mL at week 72 or later were eligible to receive intensification therapy with open-label TRUVADA (tenofovir disoproxil fumarate/emtricitabine) and results from these patients are not included as responders in this table (intensification therapy = failure). Results from the VIREAD 192 week treatment groups including these patients were 85% and 74% for HBV DNA < 400 copies/mL and 68% and 60% for normalised ALT, for study 0102 and 0103 respectively; and 34%/25% for HBeAg loss/seroconversion(study 0103 only).

When the data were evaluated including only patients that completed 192 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 VIREAD followed by open-label treatment with VIREAD; 99% and 96% of patients had HBV DNA < 400 copies/mL and 80% and 77% of patients had ALT normalisation at week 192, in studies 0102 and 0103 respectively. In study 0103, 41%/29% of patients experienced HBeAg loss/seroconversion, 11% of patients experienced HBsAg loss and 8% of patients experienced HBsAg seroconversion at week 192.

Similarly (using the on-therapy analysis), in the group of patients who received 48 weeks of double-blind treatment with HEPSEARA followed by open-label treatment with VIREAD; 100% and 99% of patients had HBV DNA < 400 copies/mL and 86% and 80% of patients had ALT normalisation, at week 192, in studies 0102 and 0103 respectively. In study 0103, 42%/35% of

Figure 4 Proportion of Patients with HBV DNA <400 copies/mL by Visit (Study 0103)



Randomised and treated patients, LTE Algorithm; 192 week data is also reported in Table 11.
 TDF: 48 weeks double-blind VIREAD followed by up to 144 weeks open-label
 ADV: 48 weeks double-blind HEPSERA followed by up to 144 weeks open-label VIREAD.

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

In a randomized, 48 week double-blind, controlled trial of VIREAD 300 mg in patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience (Study ACTG 5127), the mean serum HBV DNA levels at baseline in patients randomized to the VIREAD arm were 9.45 log₁₀ copies/mL (N=27). Treatment with VIREAD was associated with a mean change in serum HBV DNA from baseline, in the patients for whom there was 48 week data, of -5.74 log₁₀ copies/ml (N=18). In addition, 61 % of patients had normal ALT at week 48.

Experience in Patients with Persistent Viral Replication (Study 0106)

The efficacy and safety of VIREAD 300 mg or TRUVADA (tenofovir disoproxil fumarate/emtricitabine) is being evaluated in a randomised, double-blind study (Study GS-US-174-0106, 0106), in HBeAg positive and HBeAg negative patients who had persistent viraemia (HBV DNA ≥ 1000 copies/mL) while receiving HEPSERA 10 mg for more than 24 weeks. Overall at Week 48, treatment with VIREAD 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 (TRUVADA (tenofovir disoproxil fumarate/emtricitabine) were excluded. In addition, at Week 48, the percentage of patients who had ALT normalisation 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 12 below summarizes Week 48 results of patients treated with VIREAD.

Table 12. Summary of Clinical Efficacy at Week 48 (Study 0106): RAT Analysis Set

	VIREAD (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/mL¹	40 (76%)
Lamivudine-resistant patients, n/N (%) ¹	5/7 (72%)
Adefovir-resistant patients, n/N (%) ¹	7/8 (88%)
Normalised 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%)
HBsAg 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 Normalised 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.

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

Experience in Patients with Decompensated Liver Disease (Study 0108)

Study GS-US-174-0108 (0108) is a randomized, double-blind, active controlled study evaluating the safety and efficacy of VIREAD (n=45) for 48 weeks in patients with decompensated liver disease. In the VIREAD 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 coprimary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine \geq 0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/dL.

In the VIREAD 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 \geq 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-VIREAD 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 VIREAD treatment arm. The mean change from baseline in CPT score was -0.8; the mean absolute CPT score was 6 at week 48.

Clinical Resistance

Of 348 HBeAg negative and HBeAg positive patients who received treatment with VIREAD for up to 192 weeks in studies 0102 and 0103, genotypic analysis was performed on HBV isolates

for all patients with HBV DNA > 400 copies/mL (n=5). No amino acid substitutions occurred in these subjects' isolates which were associated with tenofovir resistance.

In studies 0102 and 0103, 170 patients treated with HEPSERA for 48 weeks, rolled over to treatment with VIREAD for up to 144 weeks; one patient with HBV DNA remaining > 400 copies/mL was evaluated for resistance. No amino acid substitutions were observed at sufficient frequency to establish an association with tenofovir resistance.

Among the 53 treatment-experienced patients in study 0106 treated with VIREAD, 17 had HBV DNA > 400 copies/mL following up to 48 weeks of treatment with VIREAD. 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 VIREAD for up to 48 weeks; 6 with HBV DNA > 400 copies/mL were evaluated for resistance. No amino acid substitutions associated with tenofovir resistance were identified in these isolates. In studies 0102, 0103 and 0106, 12 patients randomised to VIREAD had HBV containing lamivudine-resistance associated substitutions at baseline. Following up to 48 weeks (0106; N=7) or 96 weeks (0102 and 0103; N =5) of treatment with VIREAD, 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, 12 patients treated with VIREAD had adefovir-resistance associated substitutions at baseline. Following up to 48 weeks of treatment with VIREAD, two patients in study 0106 had HBV DNA > 400 copies/mL; no amino acid substitutions were observed in association with tenofovir resistance.

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

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

VIREAD is indicated for the treatment of chronic hepatitis B in adults.

CONTRAINDICATIONS

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

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

VIREAD should not be administered concurrently with TRUVADA (emtricitabine / tenofovir disoproxil fumarate combination tablet), ATRIPLA (tenofovir disoproxil fumarate/ emtricitabine/ efavirenz combination tablet), or HEPSERA (adefovir dipivoxil).

PRECAUTIONS

General

Patients receiving VIREAD 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 VIREAD, 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 VIREAD is not a cure for HIV infection.

HIV antibody testing should be offered to all HBV-infected patients before initiating VIREAD therapy (see PRECAUTIONS: HIV and HBV co-infection).

Use in children:

The safety and efficacy of VIREAD in paediatric patients aged 12 to <18 years is supported by data from one randomised study in which VIREAD was administered to HIV-infected treatment experienced patients (see CLINICAL TRIALS and ADVERSE EFFECTS). The safety and efficacy of VIREAD has not been established in children less than 12 years of age.

Use in the elderly:

VIREAD 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).

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 VIREAD 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 VIREAD (see ADVERSE EFFECTS- Post Marketing Experience).

VIREAD 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 VIREAD therapy. Patients at risk for, or with a history of, renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA, 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 VIREAD to any patient, and particularly to those with known risk factors for liver disease. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Drug interactions:

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. Coadministration of VIREAD with medicinal products that decrease or compete for renal clearance may increase serum concentrations of tenofovir.

VIREAD has been evaluated in healthy volunteers in combination with abacavir, didanosine, efavirenz, emtricitabine (EMTRIVA), entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives, ribavirin and tacrolimus (refer to Tables 2 and 3).

When administered with VIREAD, 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 VIREAD. Data are not available to recommend a dose adjustment of didanosine for adult or paediatric patients weighing <60 kg. When co-administered, VIREAD 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 VIREAD should be under fasted conditions.

Co-administration of VIREAD 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. VIREAD 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 VIREAD 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.

HIV and HBV co-infection:

Due to the risk of development of HIV resistance, VIREAD 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 VIREAD may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD 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-nucleoside reverse transcriptase inhibitor 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 are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Carcinogenicity and Mutagenicity:

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 times 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 times the human systemic exposure at the therapeutic dose based on AUC).

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.

Impairment of 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:

Pregnancy Category B3. No clinical data are available for pregnant women being treated with VIREAD. 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, VIREAD 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). It is not known whether tenofovir is excreted in human milk. 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.

Bone Effects:

Bone toxicities including a reduction in bone mineral density 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) or in shorter term clinical studies in paediatric patients aged 12 years and older (>1 year). However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see ADVERSE EFFECTS: Post-Marketing Experience). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

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 VIREAD-treated group compared to the placebo group. Six VIREAD treated patients and one placebo treated patient had significant (>4%) lumbar spine BMD loss in 48 weeks. Markers of bone turnover in VIREAD-treated paediatric patients 12 years of age and older suggest increased bone turnover, consistent with the bone effects observed in adults. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and fracture risk are unknown.

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.

ADVERSE EFFECTS

From Clinical Studies:

Clinical Trials in Adult Patients with HIV Infection:

More than 12,000 patients have been treated with VIREAD 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 VIREAD 300 mg once daily in Phase I-III clinical trials; over 11,000 patients have received VIREAD in expanded access studies.

Treatment-Experienced Adult Patients

Treatment-Emergent Adverse Events: The most common adverse events that occurred in patients receiving VIREAD 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 13 (below).

Table 13. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in $\geq 3\%$ in Any Treatment Group in Study 907 (0–48 weeks)

	VIREAD (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	VIREAD (N=368) (Week 0–48)	Placebo Crossover to VIREAD (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%
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, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 14 below.

Table 14. Grade 3 / 4 Laboratory Abnormalities Reported in $\geq 1\%$ of VIREAD-Treated Patients in Study 907 (0–48 weeks)

	VIREAD (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	VIREAD (N=368) (Week 0–48)	Placebo Crossover to VIREAD (N=170) (Week 24–48)
	(%)	(%)	(%)	(%)
Any \geq 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 ($\geq 3+$)	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: The adverse reactions seen in a double-blind active controlled study in which 600 treatment-naïve patients received VIREAD (N=299) or d4T (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were generally consistent, with the addition of dizziness, with those seen in treatment-experienced patients (Table 15).

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

Table 15. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 903 (0–144 weeks)

	VIREAD+3TC+EFV N=299	d4T+3TC+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 VIREAD (3%), laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and d4T treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 16.

Table 16. Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of VIREAD-Treated Patients in Study 903 (0–144 weeks)

	VIREAD+3TC+EFV N=299	d4T+3TC+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%
Neutrophil (<750/mm ³)	3%	1%
Triglyceride (>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 VIREAD + EMTRIVA administered in combination with efavirenz (N=257) or Combivir (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 17). Adverse events leading to study drug discontinuation occurred in significantly smaller number of patients in the TRUVADA (tenofovir disoproxil fumarate/emtricitabine) group compared to the Combivir 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 TRUVADA group and 6% of patients in the Combivir group.

Table 17. Frequency of Adverse Reactions to EMTRIVA and/or VIREAD (Grade 2 – 4) Occurring in ≥3% of Patients Receiving EMTRIVA and VIREAD (or TRUVADA) in Study 934 (0-144 Weeks)¹

Adverse Reaction	TRUVADA ² +EFV N=257	Combivir+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 VIREAD + EMTRIVA up to week 96 and switched to TRUVADA from week 96 to 144.

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 18).

Table 18. Grade 3/4 Laboratory Abnormalities Reported in >1% of Patients in Either Treatment Group, Study 934 (0–144 weeks)

	TRUVADA ¹ + EFV N=254	Combivir+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%
Neutrophil (<750/mm ³)	3%	5%
Triglyceride (>750 mg/dL)	5%	3%
Haemoglobin (<7.0 g/dL)	0%	2%

1. Patients received VIREAD + EMTRIVA up to week 96 and switched to TRUVADA 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 randomised study (study 321) in 87 HIV-infected paediatric patients (12 to 18 years of age) who received treatment with VIREAD (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 VIREAD 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 VIREAD 300 mg daily (n=426) or HEPSERA 10 mg daily (n=215) for 48 weeks (see Table 19).

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 ($\geq 1/100$, $< 1/10$).

Gastrointestinal disorders:

Common: nausea

Table 19. Most Frequent (>5%) Treatment-Emergent Adverse Events of Any Severity (Integrated RAT analysis set; 48-week Data from Studies 102 and 103)

AEs by Preferred Term ^a (n, %) ^b	Overall TDF (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 20.

Table 20. Grade 3/4 Laboratory Abnormalities Reported in $\geq 1\%$ of VIREAD-Treated Patients in Studies 0102 and 0103 (0-48 weeks)

	VIREAD (N=426)	HEPSERA (N=215)
Any \geq 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 ($\geq 3+$)	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 192 weeks were consistent with the safety profile of VIREAD. Grade 3/4 laboratory abnormalities were similar in nature and frequency in patients continuing treatment for up to 192 weeks in these studies.

Nucleoside-Experienced Patients: No new adverse reactions to VIREAD were identified in those patients in studies 0102, 0103 and 0106 who had been previously treated with HEPSERA, lamivudine or other nucleoside analogs (N=352).

Patients with Decompensated Liver Disease: No new adverse reactions to VIREAD were identified from a double-blind active-controlled study (0108) in which patients with decompensated liver disease received treatment with VIREAD (n=45) for 48 weeks. Among the 45 subjects receiving VIREAD, 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 ≥ 10 and MELD score ≥ 14 at entry) developed renal failure. Because both VIREAD and decompensated liver disease may have an impact on renal function, the contribution of VIREAD 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

Post-Marketing Experience:

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of VIREAD. 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,

HEPATOBIILIARY 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

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 with or without 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 with or without food.

The safety and efficacy of VIREAD in patients under the age of 12 years have not been established. VIREAD 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 VIREAD have not been established in patients over

the age of 65 years. Caution should be exercised when administering VIREAD 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 VIREAD 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, as detailed in Table 21 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 21. 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 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis ²

1. Calculated using ideal (lean) body weight.
2. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD 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 subjects with hepatic impairment compared with unimpaired subjects. No change in VIREAD dosing is required in patients with hepatic impairment.

Chronic hepatitis B: Treatment with VIREAD may be discontinued if there is HBsAg loss or HBsAg seroconversion, otherwise the optimal duration of treatment is unknown.

OVERDOSAGE

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

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 VIREAD, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

PRESENTATION

Light blue, almond-shaped film-coated tablets, debossed on one side with the markings “GILEAD” and “4331” and on the other side with the marking “300”.

VIREAD is supplied in high density polyethylene (HDPE) bottles containing 30 film-coated tablets with a desiccant (silica gel canister or sachet) and polyester fibre packing material. Each bottle is capped with a polypropylene child-resistant closure with an induction-sealed, aluminium-faced liner.

PHARMACEUTICAL PRECAUTIONS

Store below 25°C.

MEDICINES CLASSIFICATION:

PRESCRIPTION MEDICINE

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