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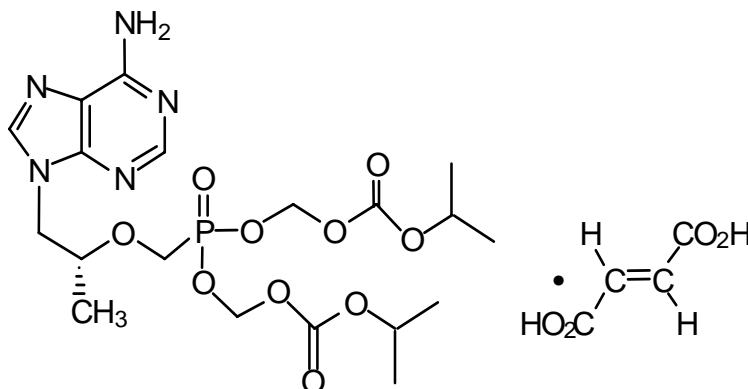
Truvada[®] (tenofovir disoproxil fumarate and emtricitabine) tablets

NAME OF THE MEDICINE

TRUVADA 300 mg tenofovir disoproxil fumarate/200 mg emtricitabine tablets.

The active substances in TRUVADA tablets are tenofovir disoproxil fumarate and emtricitabine.

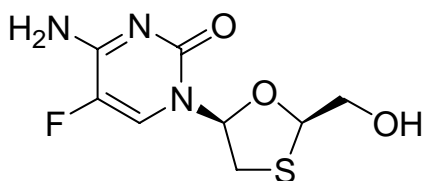
Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate is a fumaric acid salt of the *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2 [[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



CAS registry number: 202138-50-9

Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



CAS registry number: 143491-57-0

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.

Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 °C. The partition coefficient ($\log p$) for emtricitabine is -0.43 and the pKa is 2.65.

TRUVADA tablets contain the following ingredients as excipients:

Core: croscarmellose sodium, lactose, magnesium stearate (E572), microcrystalline cellulose (E460) and pregelatinised maize starch.

Coating: glycerol triacetate, hypromellose (E464), indigo carmine aluminium lake (E132), lactose, titanium dioxide (E171).

Each TRUVADA tablet is capsule-shaped and blue in colour. Each tablet is debossed on one side with the word “GILEAD” and on the other side with “701”. The tablets are supplied in bottles with screw cap closures.

PHARMACOLOGY

Tenofovir disoproxil fumarate and emtricitabine belong to the nucleoside and nucleotide reverse transcriptase inhibitors pharmacotherapeutic group (ATC code: J05AF30).

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate 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 .

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits

the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α , β , ϵ and mitochondrial DNA polymerase γ .

Antiviral activity in vitro:

Tenofovir disoproxil fumarate Plus Emtricitabine: In combination studies evaluating the in vitro antiviral activity of tenofovir and emtricitabine together, synergistic antiviral effects were observed.

Tenofovir disoproxil fumarate: The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC₅₀ (50% inhibitory concentration) values for tenofovir were in the range of 0.04–8.5 μ M. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine (3TC), stavudine (d4T), zalcitabine, zidovudine (AZT)), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G and O (IC₅₀ values ranged from 0.5–2.2 μ M). In addition, tenofovir has also been shown to be active in vitro against HIV-2, with similar potency as observed against HIV-1.

Emtricitabine: The in vitro antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC₅₀ value for emtricitabine was in the range of 0.0013–0.64 μ M (0.0003–0.158 μ g/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, 3TC, d4T, zalcitabine, AZT), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, C, D, E, F, and G (IC₅₀ values ranged from 0.007–0.075 μ M) and showed strain specific activity against HIV-2 (IC₅₀ values ranged from 0.007–1.5 μ M).

Anti-Hepatitis B Virus Activity In Vitro:

Tenofovir disoproxil fumarate: Tenofovir inhibits HBV production in HepG2 2.2.15 cells with an IC₅₀ value of 1.1 μ M.

Emtricitabine: Emtricitabine inhibits HBV production against laboratory strains of HBV with IC₅₀ values in the range of 0.01 to 0.04 μ M.

Drug Resistance:

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in vitro. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2–4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir disoproxil fumarate in combination with other antiretroviral agents. In treatment-naïve patients treated with tenofovir disoproxil fumarate + lamivudine + efavirenz through 144 weeks, viral isolates from 8/47 (17%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-naïve patients treated with emtricitabine (EMTRIVA[®]) + tenofovir disoproxil fumarate (VIREAD[®]) + efavirenz through 144 weeks, none of the HIV isolates from 19 patients analyzed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R mutation. In treatment-experienced patients, 14/304 (4.6%) of the tenofovir disoproxil fumarate-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed the K65R mutation in the HIV-1 reverse transcriptase gene.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected in vitro. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naïve patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene. In a second study in treatment-naïve patients, genotyping of viral isolates from 2/12 (17%) patients showed development of the M184V/I mutation.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized.

Tenofovir Disoproxil Fumarate: The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbours the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, d4T, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates

containing the K65R mutation, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to d4T and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

Pharmacokinetics

Pharmacokinetics in Adults: TRUVADA: One TRUVADA Tablet was bioequivalent to one VIREAD Tablet (300 mg) plus one EMTRIVA Capsule (200 mg) following single-dose administration to fasting healthy subjects (N=39).

Tenofovir disoproxil fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarised in Table 1. Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours.

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 1. Following oral administration of EMTRIVA, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02–200 µg/mL. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

Table 1. Single Dose Pharmacokinetic Parameters for Tenofovir and Emtricitabine in Adults¹

	<u>Tenofovir</u>	<u>Emtricitabine</u>
Fasted Oral Bioavailability (%)	25	93
Plasma Terminal Elimination Half-Life (hr)	17	10
C _{max} (µg/mL)	0.30 ± 0.09	1.8 ± 0.7 ²
AUC (µg*hr/mL)	2.29 ± 0.69	10.0 ± 3.1 ²
CL/F (mL/min)	1043 ± 115	302 ± 94
CL _{renal} (mL/min)	243 ± 33	213 ± 89

1. Data presented as mean values.

2. Data presented as steady state values.

Effects of Food on Oral Absorption:

TRUVADA may be administered with or without food. Administration of TRUVADA following a high fat meal (~700–1000 kcal containing 40–60% fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. An increase in tenofovir AUC of approximately 40% and an increase in C_{max} of approximately 14% were observed. Similar findings were observed when TRUVADA was administered with a light meal. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when TRUVADA was administered with either a high fat or a light meal. See DOSAGE AND ADMINISTRATION.

Age and gender:

Children and Elderly Patients: Pharmacokinetics of tenofovir and emtricitabine have not been fully evaluated in children (<18 years) or in the elderly (>65 years) (see PRECAUTIONS, Paediatric Use, Elderly Use).

Gender: Tenofovir and emtricitabine pharmacokinetics are similar in male and female patients.

Patients with Impaired Renal Function: The pharmacokinetics of tenofovir and emtricitabine are altered in subjects with renal impairment (See PRECAUTIONS, Renal Impairment). In subjects with creatinine clearance <50 mL/min, or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and AUC_{0-∞} of tenofovir and emtricitabine were increased. It is required that the dosing interval for TRUVADA be modified in patients with creatinine clearance <50 mL/min (see DOSAGE AND ADMINISTRATION).

TRUVADA should not be used in patients with creatinine clearance <30 mL/min and in patients with end-stage renal disease requiring dialysis (See PRECAUTIONS: Renal Impairment).

Patients with Hepatic Impairment: TRUVADA: The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of TRUVADA or emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Drug Interactions: TRUVADA: The drug interactions described are based on studies conducted with tenofovir disoproxil fumarate or emtricitabine as individual agents; no drug interaction studies have been conducted using TRUVADA tablets.

Tenofovir disoproxil fumarate and emtricitabine: The steady state pharmacokinetics of tenofovir and emtricitabine were unaffected when tenofovir disoproxil fumarate and emtricitabine were administered together versus each agent dosed alone.

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown the potential for CYP450 mediated interactions involving tenofovir disoproxil fumarate and emtricitabine with other medicinal products is low.

Tenofovir and emtricitabine are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of TRUVADA with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or the co-administered drug. Drugs that decrease renal function may increase serum concentrations of tenofovir and/or emtricitabine.

No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and abacavir, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, saquinavir/ritonavir and oral contraceptives. 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.. Similarly, no clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, d4T, AZT and tenofovir disoproxil fumarate.

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. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric-coated capsules significantly increases the C_{max} and AUC of

didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. Tenofovir decreases atazanavir concentration. Table 2 summarises the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine and atazanavir.

Table 2. Drug Interactions: Changes in Pharmacokinetic Parameters for Didanosine and Atazanavir 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}
Didanosine ³ enteric-coated capsules	400 once / with or without food ²	26	↑ 48–64% (↑ 25–↑ 89)	↑ 48–60% (↑ 31–↑ 79)	NC
	250 once / Simultaneously with tenofovir DF, fasted ⁴	28	↔	↑ 14 (0–↑ 31)	NC
	250 once / Simultaneously with tenofovir DF, fed ^{2,4}	28	↓ 29 (↓ 39–↓ 18)	↓ 11 (↓ 23–↑ 2)	NC
Atazanavir ⁵	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/Ritonavir ⁶ 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5) ⁶	↓ 25 (↓ 42 to ↓ 3) ⁶	↓ 23 (↓ 46 to ↑ 10) ⁶

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
2. Administration with food was with a light meal (~373 kcal, 20% fat)/.
3. See PRECAUTIONS regarding use of didanosine with tenofovir disoproxil fumarate.
4. Relative to 400 mg alone, fasted.
5. REYATAZ™ Prescribing Information (Bristol-Myers Squibb)
6. 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)

CLINICAL TRIALS

Clinical study 934, which demonstrated the safety and efficacy of EMTRIVA and VIREAD in combination with efavirenz in treatment-naïve adults, supports the use of TRUVADA tablets for the treatment of HIV-1 infection. Additional supportive data are derived from study 903, in which lamivudine (3TC) and tenofovir were used in combination in treatment-naïve adults. In clinical study 303 EMTRIVA and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens.

TRUVADA

Study 934: EMTRIVA + VIREAD + 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) 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 3.

Table 3 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	
	EMTRIVA + VIREAD + 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 EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.

In this study, EMTRIVA + VIREAD in combination with efavirenz was statistically significantly superior to lamivudine/zidovudine 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 3). The difference in the proportions of responders between the EMTRIVA + VIREAD 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 EMTRIVA + VIREAD and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The difference in the proportions of responders between the EMTRIVA + VIREAD 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 EMTRIVA + VIREAD + 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.

VIREAD (tenofovir):

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.

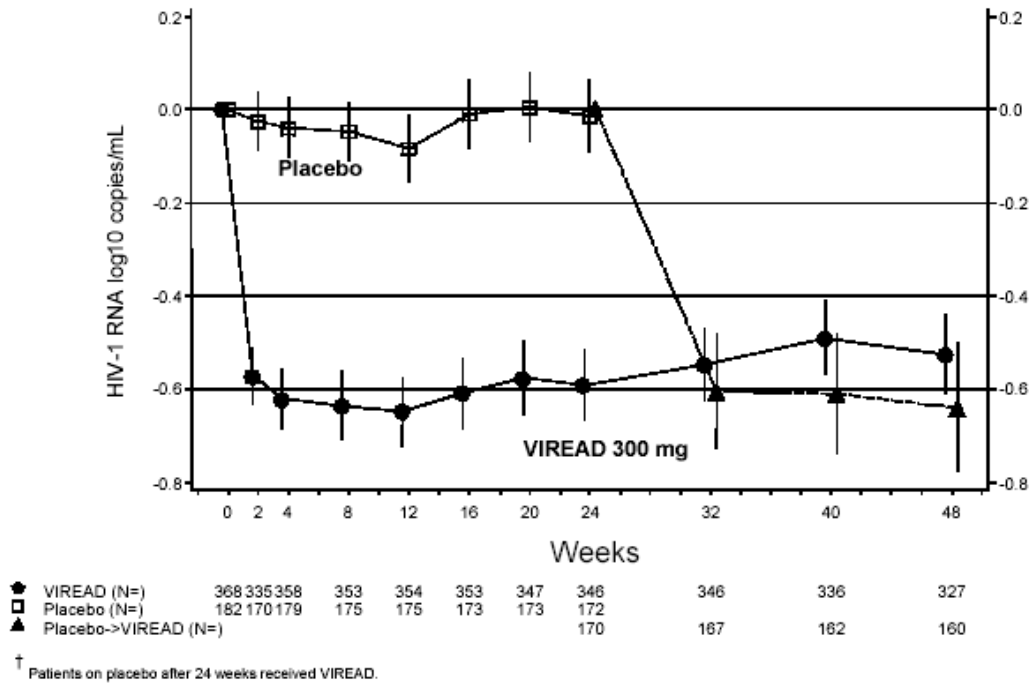
Treatment-Experienced Patients:

Study 907: Tenofovir + Standard Background Therapy (SBT) Compared With 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 RNA of 2340 (range 50–75,000) copies/mL, and mean duration of prior HIV 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 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)



The percent of patients with HIV RNA <400 copies/mL and outcomes of patients through 48 weeks are summarised in Table 4.

Table 4 Outcomes of randomised 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 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 RNA <400 copies/mL and no prior study drug discontinuation at weeks 24 and 48 respectively.
2. Patients with HIV RNA ≥ 400 copies/mL efficacy failure or missing HIV 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 RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4 counts by week 24 was +12 cells/mm³ for the tenofovir 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-Naïve 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/mL. Treatment outcomes through 144 weeks are presented in Table 5 below.

Table 5. Outcomes of Randomized Treatment (Study 903)

Outcomes	At Week 48		At Week 144	
	VIREAD+ 3TC+EFV (N=299)	d4T+3TC+E FV (N=301)	VIREAD+ 3TC+EFV (N=299)	d4T+3TC+E FV (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%

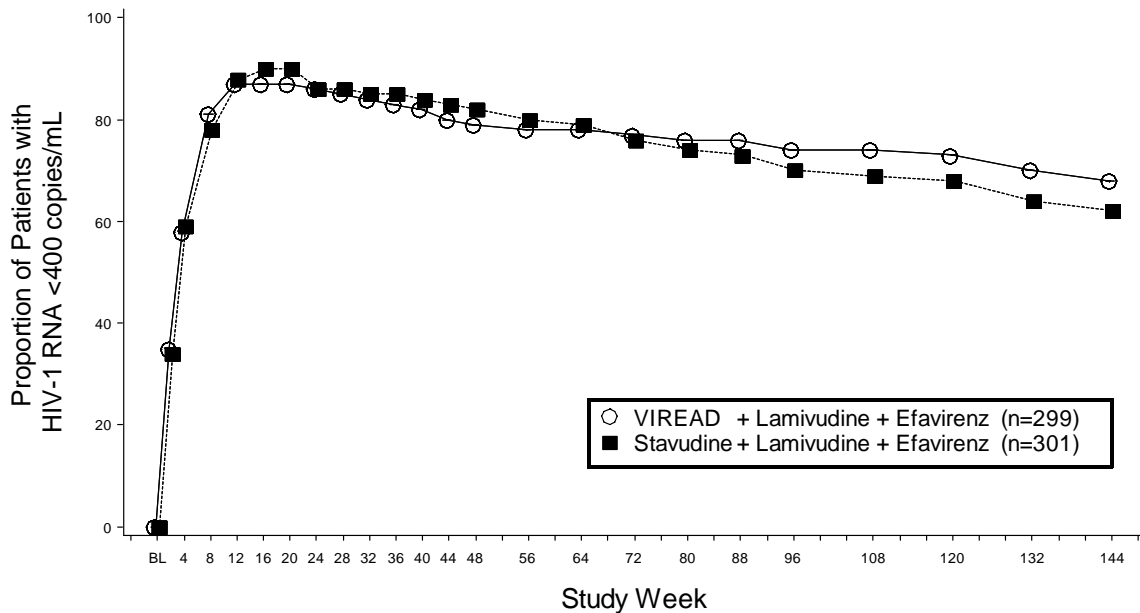
1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other 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 proportion 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
Virologic Response Through Week 144, Study 903*†



* Roche Amplicor HIV-1 Monitor Test.

† Responders at each visit are patients who had achieved and maintained HIV-1 RNA < 400 copies/mL without discontinuation by that visit.

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 6. 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 6.

Table 6. HIV RNA Response at Week 24 by Number of Baseline AZT-Associated Mutations in Studies 902 and 907 (Intent-To-Treat)¹

Number of baseline AZT-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 7 summarises the HIV RNA response by baseline VIREAD susceptibility.

Table 7. 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

EMTRIVA (emtricitabine)

Treatment-Experienced Patients:

Study 303: Emtricitabine once daily + Stable Background Therapy (SBT) Compared to Lamivudine twice daily + SBT

Study 303 was a 48 week, open-label, active-controlled multicentre study comparing emtricitabine (200 mg once daily) to lamivudine, in combination with d4T or zidovudine and a protease inhibitor or NNRTI in 440 patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV RNA ≤400 copies/mL.

Patients were randomised 1:2 to continue therapy with lamivudine (150 mg twice daily) or to switch to emtricitabine (200 mg once daily). All patients were maintained on their stable background regimen. Patients had a mean age of 42 years (range 22–80), 86% were male, 64% Caucasian, 21% African-American and 13% Hispanic. Patients had a mean baseline CD4 cell count of 527 cells/mm³ (range 37–1909), and a median baseline plasma HIV RNA of 1.7 log₁₀ copies/mL (range 1.7–4.0). The median duration of prior antiretroviral therapy was 27.6 months. Treatment outcomes through 48 weeks are presented in Table 8

Table 8. Outcomes of randomised treatment at week 48 (Study 303)

Outcome at Week 48	EMTRIVA + AZT/d4T + NNRTI/PI (N=294)	Lamivudine + AZT/d4T + NNRTI/PI (N=146)
Responder ¹	77% (67%)	82% (72%)
Virologic Failure ²	7%	8%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	4%	0%
Study Discontinuation For Other Reasons ³	12%	10%

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 mL) through week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 29 cells/mm³ for the emtricitabine arm and 61 cells/mm³ for the lamivudine arm.

Treatment-Naïve Patients:

Study 301A: Emtricitabine once daily + Didanosine once daily + Efavirenz once daily Compared to Stavudine twice daily + Didanosine once daily + Efavirenz once daily

Study 301A was a 48 week double-blind, active-controlled multicentre study comparing emtricitabine (200 mg once daily) administered in combination with didanosine and efavirenz versus d4T, didanosine and efavirenz in 571 antiretroviral naïve patients. Patients had a mean age of 36 years (range 18–69), 85% were male, 52% Caucasian, 16% African-American and 26% Hispanic. Patients had a mean baseline CD4 cell count of 318 cells/mm³ (range 5–1317) and a median baseline plasma HIV RNA of 4.9 log₁₀ copies/mL (range 2.6–7.0). Thirty-eight percent of patients had baseline viral loads >100,000 copies/mL and 31% had CD4 cell counts <200 cells/mL. Treatment outcomes through 48 weeks are presented in Table 9.

Table 9. Outcomes of randomised treatment at week 48 (Study 301A)

Outcome at Week 48	EMTRIVA + Didanosine + Efavirenz (N=286)	d4T + Didanosine + Efavirenz (N=285)
Responder ¹	81% (78%)	68% (59%)
Virologic Failure ²	3%	11%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	7%	13%
Study Discontinuation For Other Reasons ³	9%	8%

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 168 cells/mm³ for the emtricitabine arm and 134 cells/mm³ for the d4T arm.

INDICATIONS

TRUVADA is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of VIREAD and EMTRIVA in treatment-naïve and treatment-experienced adults.

CONTRAINDICATIONS

TRUVADA is contraindicated in patients with known hypersensitivity to tenofovir, tenofovir disoproxil fumarate, emtricitabine or any other components of the tablet.

TRUVADA must not be administered to children or adolescents under the age of 18 years.

TRUVADA is a fixed-dose combination of tenofovir disoproxil fumarate and emtricitabine. TRUVADA should not be administered concomitantly with VIREAD (tenofovir disoproxil fumarate), EMTRIVA (emtricitabine), ATRIPLA (tenofovir disoproxil fumarate/emtricitabine/efavirenz combination tablet), drugs containing lamivudine, including Combivir, 3TC, Zeffix, Kivexa or Trizivir, or with HEPSERA (adefovir dipivoxil).

PRECAUTIONS

General

Patients receiving TRUVADA 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 TRUVADA, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that TRUVADA is not a cure for HIV infection.

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, in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised

when administering nucleoside analogues to any patient with known risk factors for liver disease, however, cases have also been reported in patients with no known risk factors. Treatment with TRUVADA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment

Tenofovir and emtricitabine are principally eliminated by the kidney. Dosing interval adjustment of TRUVADA is required in all patients with creatinine clearance <50 mL/min, (see DOSAGE AND ADMINISTRATION). Renal function should be closely monitored in these patients. The safety and efficacy of TRUVADA therapy have not been established in patients with creatinine clearance between 30 and 49 ml/min, and so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity. TRUVADA should not be administered to patients with creatinine clearance <30 mL/min or patients requiring haemodialysis.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of VIREAD (see ADVERSE EFFECTS, Post Marketing Surveillance). TRUVADA 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 TRUVADA therapy. Patients at risk for, or with a history of, renal dysfunction should be routinely monitored for changes in serum creatinine and phosphorus.

Drug Interactions

Tenofovir disoproxil fumarate: When tenofovir disoproxil fumarate was administered with didanosine the 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 2). 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 adults weighing ≥ 60 kg, the didanosine dose should be reduced to 250 mg daily when it is co-administered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg.

When co-administered, TRUVADA 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 TRUVADA should be under fasted conditions. **Co-administration of TRUVADA 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 (see Table 2). TRUVADA 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 and emtricitabine are primarily eliminated by the kidneys, co-administration of TRUVADA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or other renally eliminated drugs.

Bone Effects

Bone toxicities including a reduction in bone mineral density have been observed in tenofovir disoproxil fumarate studies in three animal species. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) of VIREAD. However, bone abnormalities (infrequently contributing to fractures) 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.

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Patients with HIV and Hepatitis B Virus (HBV) Co-infection

Discontinuation of TRUVADA therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients with HIV infection co-infected with HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping TRUVADA treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation 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.

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-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.

Carcinogenicity and Mutagenicity

No carcinogenicity studies have been conducted with tenofovir disoproxil fumarate and emtricitabine in combination. 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).

In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

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. Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in mouse micronucleus test *in vivo*.

Impairment of fertility

No reproductive toxicity studies have been conducted with tenofovir disoproxil fumarate and emtricitabine in combination. 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 expected 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.

Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50-80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

Use in Pregnancy

Pregnancy Category B3

No clinical data are available for pregnant women being treated with tenofovir disoproxil fumarate or emtricitabine. No embryofoetal development studies have been conducted with tenofovir disoproxil fumarate and emtricitabine in combination.

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. No evidence of embryofoetal toxicity or teratogenicity was observed in mice or rabbits at respective emtricitabine exposures (AUC) of 50 and 130 fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse foetal effects. Because animal reproduction studies are not

always predictive of human response, TRUVADA should be used during pregnancy only if clearly needed.

Use in Lactation

It is not known whether tenofovir or emtricitabine are excreted in human milk. Because of the potential for HIV transmission and for serious adverse reactions in nursing infants, mothers should be instructed not to breast feed if they are receiving TRUVADA.

Use in Children

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Clinical studies of tenofovir and emtricitabine did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. 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).

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

ADVERSE EFFECTS

Four hundred and forty seven HIV-1 infected patients have received combination therapy with EMTRIVA and VIREAD with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 48 weeks in ongoing clinical studies.

Study 934 - Treatment Emergent Adverse Events: Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either EMTRIVA + VIREAD 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 10). Adverse events leading to study drug discontinuation occurred in significantly smaller number of patients in the TRUVADA 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 10 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 EMTRIVA + VIREAD 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 11).

Table 11 Grade 3/4 Laboratory Abnormalities Reported in >1% of Patients of 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%	2%
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 EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.

VIREAD

From Clinical Studies

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 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 12 (below).

Table 12. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥ 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 13 below.

Table 13. Grade 3 / 4 Laboratory Abnormalities Reported in ≥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 ≥ 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 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 14).

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

Table 14. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 903 (0–144 weeks)

	VIREAD+3TC+EFV	d4T+3TC+EFV
	N=299	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 15.

Table 15. Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of VIREAD-Treated Patients in Study 903 (0–144 weeks)

	VIREAD+3TC+EFV	d4T+3TC+EFV
	N=299	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%

From Post Marketing Surveillance

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

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

Asthaenia

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 DF therapy in the absence of proximal renal tubulopathy.

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)).

EMTRIVA

More than 2000 adult patients with HIV infection have been treated with EMTRIVA alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 303 and 301A in which 440 treatment experienced (303) and 571 treatment naïve (301A) patients received EMTRIVA 200 mg (N=580) or comparator drug (N=431) for 48 weeks.

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials were headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies because of to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the adverse reactions reported in adults, anaemia has been reported commonly and hyperpigmentation very commonly, in paediatric patients.

A summary of EMTRIVA treatment emergent clinical adverse events in studies 303 and 301A is provided in Table 16.

Table 16. Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in $\geq 3\%$ of EMTRIVA-Treated Patients in Either Study 303 or 301A (0-48 Weeks)

	303		301A	
	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	EMTRIVA + Didanosine + Efavirenz (N=286)	Stavudine + Didanosine + Efavirenz (N=285)
Body as a Whole				
Abdominal Pain	8%	11%	14%	17%
Asthenia	16%	10%	12%	17%
Headache	13%	6%	22%	25%
Digestive System				
Diarrhoea	23%	18%	23%	32%
Dyspepsia	4%	5%	8%	12%
Nausea	18%	12%	13%	23%
Vomiting	9%	7%	9%	12%
Musculoskeletal				
Arthralgia	3%	4%	5%	6%
Myalgia	4%	4%	6%	3%
Nervous System				
Abnormal Dreams	2%	<1%	11%	19%
Depressive Disorders	6%	10%	9%	13%
Dizziness	4%	5%	25%	26%
Insomnia	7%	3%	16%	21%
Neuropathy/Peripheral Neuritis	4%	3%	4%	13%
Paresthaesia	5%	7%	6%	12%
Respiratory				
Increased Cough	14%	11%	14%	8%
Rhinitis	18%	12%	12%	10%
Skin				
Rash Event ¹	17%	14%	30%	33%

1. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

Laboratory Abnormalities:

Laboratory abnormalities observed in the EMTRIVA studies occurred with similar frequency in the treatment and placebo-treated/comparator groups.

A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 17.

Table 17. Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥1% of EMTRIVA-Treated Patients in Either Study 303 or 301A

	303		301A	
	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	EMTRIVA + Didanosine + Efavirenz (N=286)	d4T + Didanosine + Efavirenz (N=285)
Percentage with Grade 3 or Grade 4 laboratory abnormality	31%	28%	34%	38%
ALT (>5.0 x ULN ¹)	2%	1%	5%	6%
AST (>5.0 x ULN)	3%	<1%	6%	9%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine Kinase (>4.0 x ULN)	11%	14%	12%	11%
Neutrophils (<750 mm ³)	5%	3%	5%	7%
Pancreatic Amylase (>2.0 x ULN)	2%	2%	<1%	1%
Serum Amylase (>2.0 x ULN)	2%	2%	5%	10%
Serum Glucose (<40 or >250 mg/dL)	3%	3%	2%	3%
Serum Lipase (>2.0 x ULN)	<1%	<1%	1%	2%
Triglycerides (>750 mg/dL)	10%	8%	9%	6%

1. ULN=Upper limit of normal.

From Post Marketing Surveillance

No additional events have been identified for inclusion in this section.

TRUVADA

From Post Marketing Surveillance

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).

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of TRUVADA is one tablet (containing 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine), taken orally, once daily with or without food.

Children: The safety and efficacy of TRUVADA and tenofovir disoproxil fumarate (one of the components of TRUVADA) have not been established in patients under the age of 18 years. Consequently, TRUVADA should not be administered to children or adolescents.

Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal Insufficiency: Significantly increased drug exposures occurred when VIREAD or EMTRIVA were administered to patients with moderate to severe renal impairment (See VIREAD and EMTRIVA Data Sheet). Therefore, the dosing interval of TRUVADA should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 18. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated, therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 18. Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) ^a		
	≥50	30–49	<30 (Including Patients Requiring Haemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA should not be administered.

^a Calculated using ideal (lean) body weight.

Hepatic impairment: The pharmacokinetics of TRUVADA or emtricitabine have not been studied in subjects with hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment. Emtricitabine is not significantly metabolised by liver enzymes, so the impact of hepatic impairment should be limited.

OVERDOSAGE

There is no known antidote for TRUVADA. If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir disoproxil fumarate

Clinical experience of doses higher than the therapeutic dose of tenofovir disoproxil fumarate 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.

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.

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology study, single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

PRESENTATION AND STORAGE CONDITIONS

TRUVADA is available as tablets. Each tablet contains 300 mg tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), and 200 mg emtricitabine. The tablets are blue, capsule-shaped, film-coated, debossed with “GILEAD” on one side and with “701” on the other side.

TRUVADA is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a desiccant (silica gel canister or sachet) and is closed with a screw cap closure.

Store below 25 °C.

MEDICINE CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF THE SPONSOR

Gilead Sciences (NZ)
Level 35, 23-29 Albert Street
Auckland
New Zealand

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