VIREAD®

(tenofovir disoproxil fumarate) Tablets

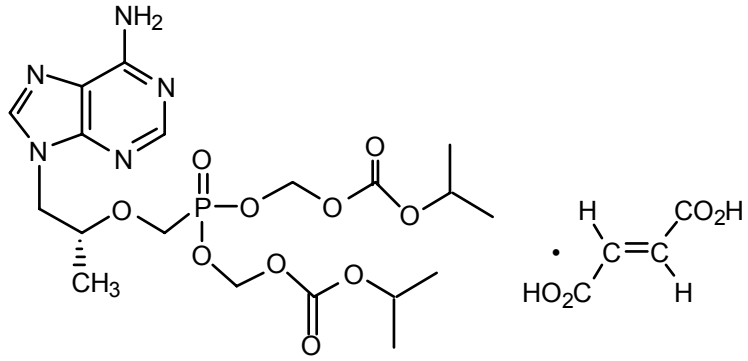
RxOnly

WARNING
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

VIREAD is the brand name for tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

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 $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (*log p*) of 1.25 at 25°C.

VIREAD tablets are for oral administration. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with a light blue colored film (Opadry II Y-30-10671-A) that is made of FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

Microbiology

Mechanism of Action: 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.

Antiviral Activity In Vitro: 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 IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04 µM to 8.5 µM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5 µM to 2.2 µM).

Drug Resistance: 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 3-4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral agents. In treatment-naïve patients treated with Viread + lamivudine + efavirenz, viral isolates from 7/29 (24%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-experienced patients, 14/304 (4.6%) of the VIREAD-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. 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 harbors the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Pharmacokinetics

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: VIREAD is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from VIREAD in fasted patients is 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.

The pharmacokinetics of tenofovir are dose proportional over a VIREAD dose range of 75 to 600 mg and are not affected by repeated dosing.

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 $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of VIREAD with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. 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: In vitro binding of tenofovir to human plasma or serum proteins is 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 and Elimination: In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of VIREAD 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

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

Special Populations:

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Tenofovir pharmacokinetics are similar in male and female patients.

Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (>65 years).

The pharmacokinetics of tenofovir have not been studied in patients with hepatic impairment; however, tenofovir is not metabolized by liver enzymes, so the impact of liver impairment should be limited (See PRECAUTIONS, Hepatic Impairment).

The pharmacokinetics of tenofovir are altered in patients with renal impairment (See WARNINGS, Renal Impairment). In patients 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 recommended 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 ± 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)	12-28 (N=11)
C_{max} (ng/mL)	335.4 ± 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 ± 115.4	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 hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

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, indinavir, lamivudine, lopinavir/ritonavir, methadone and oral contraceptives. Tables 2 and 3 summarize pharmacokinetic effects of co-administered drug on tenofovir pharmacokinetics and effects of VIREAD on the pharmacokinetics of co-administered drug.

Table 4 summarizes 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.

Table 2. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] 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
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
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)

1. Patients received VIREAD 300 mg once daily
2. Increase = ↑ ; Decrease = ↓; No Effect = ⇔, NC = Not Calculated

Following multiple dosing to HIV-negative subjects receiving 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.

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
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
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	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Methadone[2]	40-110 once daily X 14 days[3]	13	⇔	⇔	⇔
Oral Contraceptives[4]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	⇔	⇔	⇔
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔

1. Increase = ↑; Decrease = ↓; No Effect = ⇔, NA = Not Applicable
2. R-(active), S-and total methadone exposures were equivalent when dosed alone or with VIREAD
3. Individual subjects were maintained on their stable metahdone dose. No pharmcodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported
4. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD

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)

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

INDICATIONS AND USAGE

VIREAD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication 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.

Additional important information regarding the use of VIREAD for the treatment of HIV-1 infection:

- There are no study results demonstrating the effect of VIREAD on clinical progression of HIV-1.
- The use of VIREAD should be considered for treating adult patients with HIV-1 strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history. (See Description of Clinical Studies)

Description of Clinical Studies

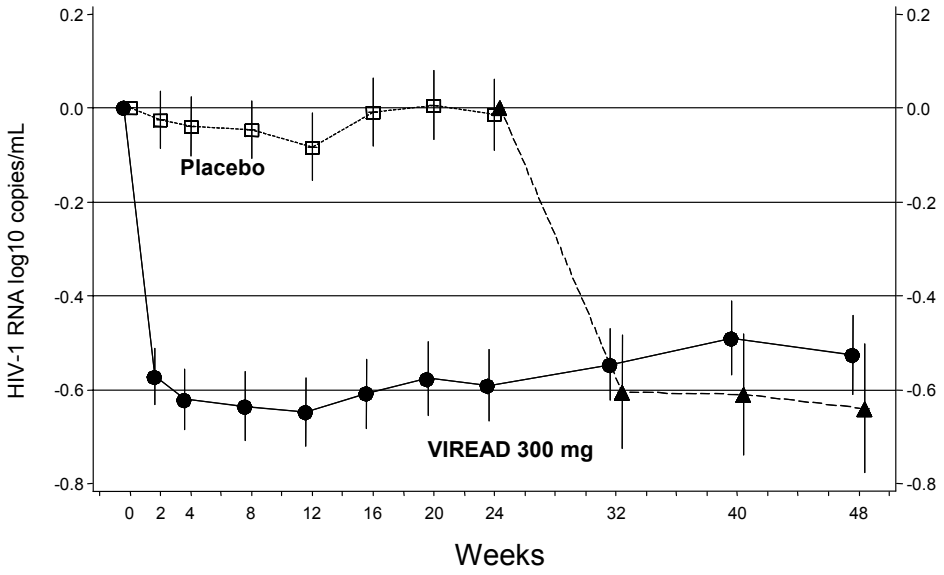
Treatment-Experienced Patients:

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

Study 907 was a 24 week, double-blind placebo-controlled multicenter 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/mm^3 (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 log_{10} copies/mL plasma HIV-1 RNA levels over time up to week 48 are presented below in Figure 1.

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



⬟ 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.

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

Table 5. Outcomes of Randomized Treatment (Study 907)

Outcomes	0-24 weeks		0-48 weeks	24-48 weeks
	VIREAD (N=368) %	Placebo (N=182) %	VIREAD (N=368) %	Placebo Crossover to VIREAD (N=170) %
HIV-1 RNA <400 copies/mL[1]	40%	11%	28%	30%
Virologic failure[2]	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons[3]	3%	3%	5%	1%

[1] Patients with HIV-1 RNA <400 copies/mL and no prior study drug discontinuation at Week 24 and 48, respectively
[2] Patients with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV –1 RNA at Week 24 and 48 respectively
[3] Includes lost to follow up, patient withdrawal, noncompliance, protocol violation and other reasons.

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/mm^3 for the VIREAD group and -5 cells/mm^3 for the placebo group. Mean change in absolute CD4 counts by week 48 was +4 cells/mm^3 for the VIREAD group.

Through week 24, one patient in the VIREAD group and no patients in the placebo arm experienced a new CDC Class C event.

Treatment-Naïve Patients

Study 903: VIREAD + Lamivudine +Efavirenz Compared to Stavudine + Lamivudine + Efavirenz

Data through 48-weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing VIREAD (300 mg QD) administered in combination with lamivudine and efavirenz versus stavudine, lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18 to 64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4 cell count was 279 cells/mm^3 (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 48 weeks are presented in Table 6 below.

Table 6. Outcomes of Randomized Treatment at Week 48 (Study 903)

Outcome at Week 48	VIREAD+3TC+EFV (N=299) %	Stavudine+3TC+EFV (N=301) %
Responder[1]	79%	82%
Virologic failure[2]	6%	4%
Rebound	5%	3%
Never suppressed through Week 48	0%	1%
Added an antiretroviral agent	1%	1%
Death	<1%	1%
Discontinued due to adverse event	6%	6%
Discontinued for other reasons[3]	8%	7%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48
2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48
3 Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at week 48 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (< or >100,000 copies/mL) and CD4 cell count (< or ≥ 200 cells/mm^3). Through 48 weeks of therapy, 76% and 79% of patients in the VIREAD and stavudine arms, respectively achieved HIV-1 RNA < 50 copies/mL. The mean increase from baseline in CD4 cell count was 169 cells/mm^3 for the VIREAD arm and 167 cells/mm^3 for the stavudine arm.

Through 48 weeks, eight patients in the VIREAD group and six patients in the stavudine group experienced a new CDC Class C event.

Genotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy

The virologic response to VIREAD therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment experienced patients participating in two controlled trials.

The use of resistance testing and the clinical interpretation of genotypic mutations is a complex and evolving field. Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

In two clinical studies, 94% of the participants evaluated had baseline HIV-1 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 study results.

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Descriptions of numerical

differences in HIV-1 RNA response are displayed in Table 7. Because of the large number of potential comparisons, statistical testing was not conducted.

Varying degrees of cross-resistance of VIREAD to pre-existing zidovudine-associated mutations were observed and appeared to depend on the number of specific mutations. VIREAD-treated patients whose HIV-1 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-1 RNA responses by number and type of baseline zidovudine-associated mutations are shown in Table 7.

Table 7. HIV-1 RNA Response at Week 24 by Number of Baseline Zidovudine-Associated Mutations (Intent-To-Treat)[1]

Number of baseline zidovudine-associated mutations[2]	Change in HIV-1 RNA[3] (N)	
	VIREAD 300 mg	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=1 RNA change from baseline through week 24 ($DAVG_{24}$) in log_{10} copies/mL

In the protocol defined analyses, virologic response to VIREAD was not reduced in patients with HIV-1 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-1 RNA relative to placebo. In the presence of zidovudine-associated mutations, the M184V mutation did not affect the mean HIV-1 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 the K65R mutation appeared to have reduced virologic responses to VIREAD.

The presence of at least one HIV-1 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-1 protease inhibitors is unlikely because of the different enzyme targets involved.

Phenotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy

The virologic response to VIREAD therapy has been evaluated with respect to baseline phenotype (N=100) in treatment-experienced patients participating in two controlled trials. Phenotypic analysis of baseline HIV-1 from patients in these studies demonstrated a correlation between baseline susceptibility to VIREAD and response to VIREAD therapy. Table 8 summarizes the HIV-1 RNA response by baseline VIREAD susceptibility.

Table 8. HIV-1 RNA Response at Week 24 by Baseline VIREAD Susceptibility (Intent-To-Treat)[1]

Baseline VIREAD Susceptibility[2]	Change in HIV-1 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-1 RNA change from baseline through week 24 ($DAVG_{24}$) in log_{10} copies/mL

CONTRAINDICATIONS

VIREAD is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

WARNINGS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. 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 analogs 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 VIREAD 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 is principally eliminated by the kidney. Dosing interval adjustment is recommended in all patients with creatinine clearance < 50 mL/min (see DOSAGE AND ADMINISTRATION). No safety data are available in patients with renal dysfunction who received VIREAD using these dosing guidelines.

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 Reactions- Post Marketing Experience). The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents, however, some cases occurred in patients without identified risk factors.

VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

Patients with HIV and Hepatitis B Virus Coinfection

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. VIREAD is not indicated for the treatment of chronic HBV infection and the safety and efficacy of VIREAD have not been established in patients co-infected with HBV and HIV. Exacerbations of HBV have been reported in patients after the discontinuation of VIREAD. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow up for at least several months after stopping VIREAD treatment.

PRECAUTIONS

Drug Interactions

When administered with VIREAD, C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly (see Table 4). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. In adults weighing >60kg, the didanosine dose should be reduced to 250mg when it is co-administered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for 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.**

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. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

Bone Effects

In study 903 through 48 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At 48 weeks, percent decreases in BMD from baseline (mean ± SD) were greater in

patients receiving VIREAD + lamivudine + efavirenz (spine, -3.3% ± 3.9 ; hip, –3.2% ± 3.6) compared with patients receiving stavudine + lamivudine + efavirenz (spine, -2.0 ± 3.5; hip. -1.8% ± 3.3). The proportion of patients who met a protocol defined value of BMD loss (5% decrease in spine or 7% decrease in hip) was higher in the VIREAD group than the stavudine group. In addition, there were significant increases in levels of four biochemical markers of bone metabolism (serum bone – specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels were also higher in the VIREAD group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. There was one bone fracture reported in the VIREAD group compared with four in the stavudine group; no pathologic fractures were identified over 48 weeks of study treatment. The clinical significance of the changes in BMD and biochemical markers is unknown and follow-up is continuing to assess long-term impact.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at substantial risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be considered for HIV-associated osteopenia or osteoporosis. If bone abnormalities are suspected then appropriate consultation should be obtained.

Hepatic Impairment

The pharmacokinetics of tenofovir have not been studied in patients with hepatic impairment. As tenofovir and tenofovir disoproxil are not metabolized by liver enzymes, the impact of liver impairment should be limited.

Fat Redistribution

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

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies of tenofovir disoproxil fumarate in rats and mice are in progress.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male and female rats at a dose equivalent to 19 times the human dose based on body surface area comparisons. There was, however, an alteration of the estrous cycle in female rats.

Pregnancy

Pregnancy category B: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD.**

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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.

ADVERSE REACTIONS

Clinical Trials: 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 1,287 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, diarrhea, 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 9 (below).

Table 9. 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				
Diarrhea	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 10 below.

Table 10. 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: >990U/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 comparative controlled study in which 600 treatment-naïve patients received VIREAD (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 48 weeks (Study 903) were generally consistent, with the addition of dizziness, with those seen in treatment-experienced patients (Table 11).
Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea and nausea.

Table 11. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥ 3% in Any Treatment Group in Study 903 (0–48 weeks)

	VIREAD+3TC+EFV	d4T+3TC+EFV
	N=299	N=301
Body as a Whole		
Headache	10%	11%
Pain	7%	6%
Fever	5%	6%
Abdominal Pain	4%	8%
Back Pain	4%	3%
Asthenia	3%	5%
Digestive System		
Diarrhea	6%	6%
Nausea	5%	6%
Dyspepsia	3%	2%
Vomiting	3%	6%
Musculoskeletal		
Arthralgia	2%	4%
Nervous System		
Depression	7%	5%
Insomnia	4%	6%
Abnormal Dreams	3%	3%
Dizziness	3%	5%
Paresthesia	2%	3%
Peripheral neuropathy[1]	1%	4%
Respiratory		
Pneumonia	3%	3%
Skin and Appendages		
Rash Event[2]	15%	11%

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 stavudine group (8%) compared with VIREAD (2%), laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 12.

Table 12. Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of VIREAD-Treated Patients in Study 903 (0–48 weeks)

	VIREAD+3TC+EFV	d4T+3TC+EFV
	N=299	N=301
Any ≥ Grade 3 Laboratory Abnormality	28%	31%
Creatine Kinase (M: >990 U/L) (F:>845 U/L)	8%	9%
Serum Amylase (>175 U/L)	7%	6%
AST (M: >180 U/L) (F: >170 U/L)	4%	5%
ALT (M: >215 U/L) (F: >170 U/L)	4%	4%
Hematuria (>100 RBC/HPF)	4%	4%
Neutrophil (<750/mm^3)	3%	1%
Triglyceride (>750 mg/dL)	2%	8%

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 they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting or potential causal connection to VIREAD.

IMMUNE SYSTEM DISORDERS
Allergic reaction

METABOLISM AND NUTRITION DISORDERS
Hypophosphatemia, Lactic acidosis

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS
Dyspnea

GASTROINTESTINAL DISORDERS
Abdominal pain, Pancreatitis

RENAL AND URINARY DISORDERS
Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis

OVERDOSAGE

Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

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

DOSAGE AND ADMINISTRATION

The dose of VIREAD is 300 mg once daily taken orally, without regard to food.

Dose Adjustment for Renal Impairment:

Significantly increased drug exposures occurred when VIREAD was administered to patients with moderate to severe renal impairment (See PHARMACOKINETICS). The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the recommendations in Table 13. 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 13. Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			**Hemodialysis Patients**
	≥ 50	**30–49**	**10–29**	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Twice a week	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a Calculated using ideal (lean) body weight.
b 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-hemodialysis patients with creatinine clearance < 10 mL/min; therefore, no dosing recommendation is available for these patients.

HOW SUPPLIED

VIREAD is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-shaped, light blue, film-coated, and debossed with “GILEAD” and “4331” on one side and with “300” on the other side. They are packaged as follows: Bottles of 30 tablets (NDC 61958-0401-1) containing a desiccant (silica gel canister or sachet) and closed with child-resistant closure.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature).

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August 2003

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